The Journal of Obstetrics and Gynaecology of the British Empire

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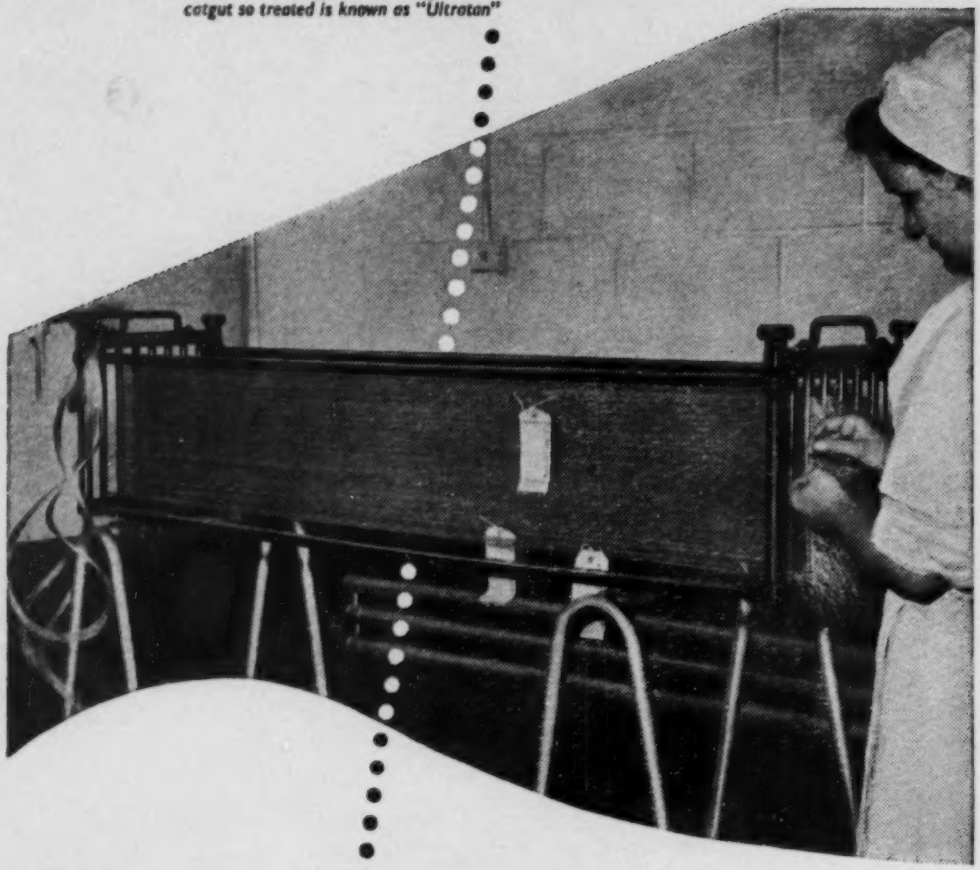

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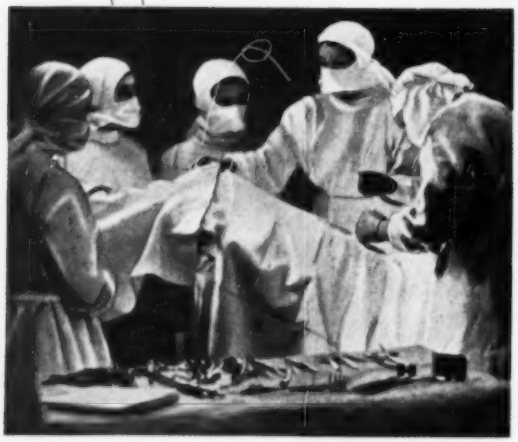

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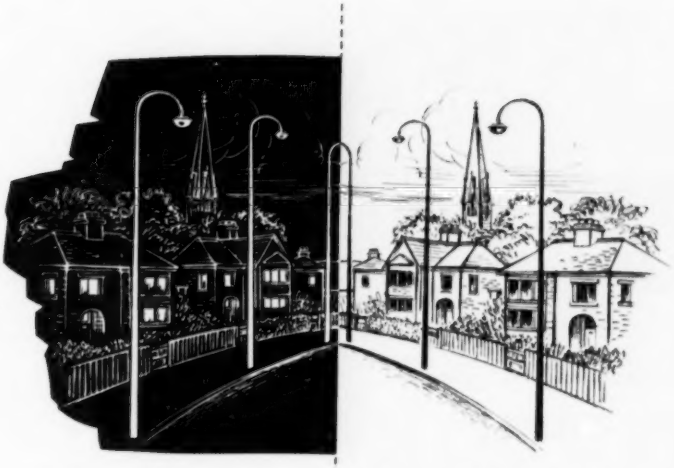

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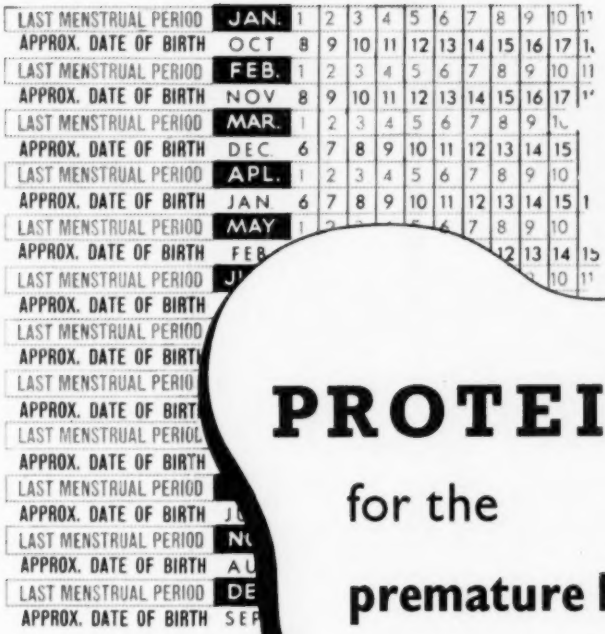
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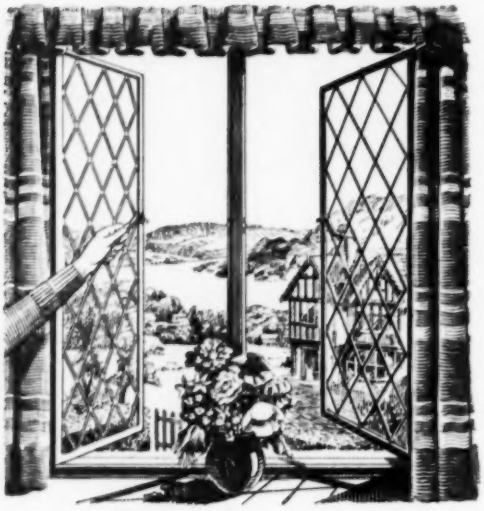

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[1] O'Sullivan, *The Practitioner*, No. 986, August 1950

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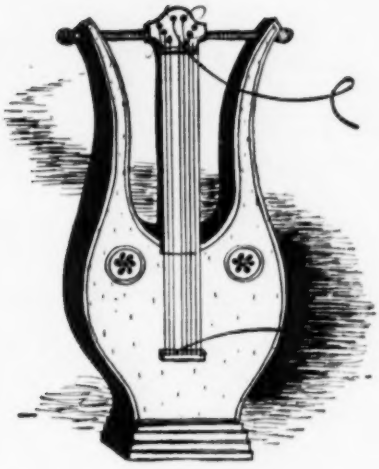

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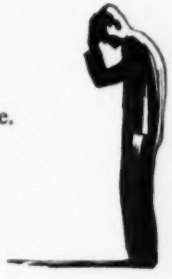

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THE MATERNAL PLACENTAL BLOOD FLOW IN NORMOTENSIVE AND HYPERTENSIVE WOMEN

BY

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KNOWLEDGE of the haemodynamics of the human placenta, though it has progressed much, is still far from complete. Kellar (1950) and his co-workers have recently filled some of the gaps in regard to the circulation generally, but the dual blood system of the placenta has remained an enigma, largely because of the difficulties encountered in its study *in vivo*.

Barcroft (1946) and his collaborators have made a series of observations on the foetal placental blood flow in the sheep, but the data thus obtained gave only indirect information as to the maternal blood flow, and the deductions made in this way are open to criticism. In addition there is considerable doubt as to whether pregnancy toxaemia in sheep is analogous to the human condition.

A direct study of the human maternal blood flow has therefore become an urgent necessity, especially in view of the recent concentration of ideas (Bastiaanse and Mastboom, 1949; Beker 1948, etc.) involving a supposed placental ischaemia as the trigger in the initiation of pre-eclamptic toxaemia. These recent concepts, however, are not far removed from the "red infarct" theory of Young (1914).

With the purpose of demonstrating the presence (or absence) of such a placental ischaemia, a method has been evolved whereby the relative rates of maternal placental blood flow in normal and hypertensive women can be studied, the results being presented below. The method depends on the use of radio-active sodium, Na^{24}, as a tracer substance.

THEORETICAL CONSIDERATIONS

Fig. 1 represents schematically the assumptions which are made concerning the placental circulation. In the first method, the tracer substance, in this case Na^{24}, is administered intravenously, and the arterial blood entering the placenta at rate v ml./minute has a concentration C_A per ml., the concentration being measured in arbitrary units. During its passage through the placenta the maternal blood loses a quantity dQ of its Na^{24} content by transfer across the placental barrier to the foetal circulation, so that the venous blood leaving has a reduced Na^{24} concentration C_v. It is therefore possible in principle to

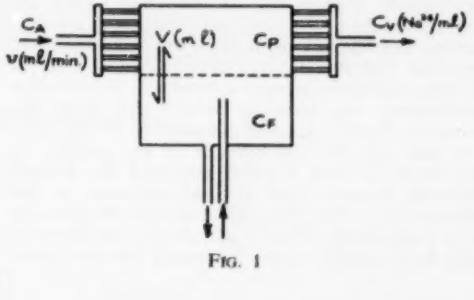

FIG. 1

determine the placental blood flow v by an arterio-venous difference method, utilizing the equation

$$dQ=(C_A-C_v)v.dt \quad \ldots\ldots(1)$$

It will be shown below that practical difficulties precluded the use of this method.

The alternative method which presents itself involves the administration of a small quantity N_o of the tracer substance directly into the maternal placental "pool", which is assumed to have an effective volume V. Provided that mixing is essentially complete, the amount N remaining in the placenta after a time t should be given by equation:

$$N=N_o e^{-\frac{v}{V}t} \quad \ldots\ldots(2)$$

Consequently, provided a number of assumptions are made, it is apparent that changes in placental blood flow should be reflected by changes in the disappearance rate of a test injection.

The Arterio-venous Difference Method

Attempts were made to utilize this method in the early stages of this work. The arterial concentration of Na^{24} at a given time was determined from a blood sample obtained from the brachial artery. Since there was no particular vein which could be assumed to be draining placental blood alone, a sample of blood was taken from the placental pool itself, and the concentration Cp of Na^{24} assumed to represent the mean of the arterial and venous concentrations. The measurements were carried out on patients undergoing Caesarean section at or near term, so that the infant would be delivered within a relatively short period after the intravenous administration of Na^{24}.

The amount of Na^{24} transferred to the foetal circulation in time t was determined by the method employed by Flexner and his associates (1948). About 3 hours after delivery, a sample of the infant's blood was obtained via a polythene catheter in the umbilical vein, the plasma Na^{24} measured, and the infant's Na^{24} content calculated on the assumption that the "sodium space" corresponded to 43.5 per cent of the body weight (Flexner *et al.*, 1947). Recent work on the assay of radio-activity in bulky samples (Veall and Vetter, 1952) and in laboratory animals (Arnott and Fossey, 1952), by means of a suitable array of gamma-ray counters suggests that the same technique could well be applied to the problem of the measurement of gamma-emitting isotopes in newborn infants. Apart from the fact that a direct measurement is obtained of total radioactive content without any physiological assumptions, the technique would also avoid the necessity of taking a blood sample from the infant.

It was not the measurement of the quantity Q transferred in time t which presented the greatest difficulty, however, but the determination of the difference C_A-Cp. For some time after the injection of a tracer dose of Na^{24}, the plasma concentration falls fairly rapidly as the ion passes into the extracellular fluid and elsewhere in the body. Consequently appreciable errors can occur if the arterial and placental maternal blood samples are not taken exactly simultaneously. It was found that even when this and other experimental errors were reduced as far as practicable under the prevailing conditions, it was still not possible to measure the difference C_A-Cp with any degree of precision, mainly because the difference was a relatively small one—apparently less than 10 per cent. Attempts to use this method for measuring maternal placental blood flow were therefore soon abandoned, and the following method employed.

Measurement of Na^{24} Disappearance Rate

The patients investigated were 38 weeks pregnant or more, and were admitted to hospital.

The placenta was first located using the radioactive sodium method (Browne and Veall, 1950). When the placenta was found to be situated partly or wholly on the anterior uterine wall, the case was considered suitable for further investigation. Three days were allowed to elapse so that residual radioactivity would be so low as not to interfere with subsequent measurements. During this period the blood-pressure was recorded twice daily so as to obtain a mean level.

With the bladder empty a small subcutaneous wheal was raised over the desired point by infiltration with 2 per cent procaine, and through this a larger needle (18 S.W.G.), with procaine syringe attached, was introduced to continue procaine infiltration until the chorio-decidual space was reached. This was determined by repeatedly withdrawing the plunger till free back-flow of blood occurred. With experience it was possible to appreciate the various layers through which the needle passed, and thus to gauge whether back-flow of blood was encountered when the needle entered the placenta, and not before. A small volume (about 1 ml.) of normal saline containing 10 microcuries of radioactive sodium was then injected, taking care that the point of the needle was not moved. The needle was withdrawn without delay, and a Geiger counter tube (Type GM4 with β-ray screen over window) was placed immediately over the site of the injection. The counter tube was connected with a Probe Unit Type 1014A to a counting ratemeter 1036A or its equivalent, the output of the latter being fed to a 0–5

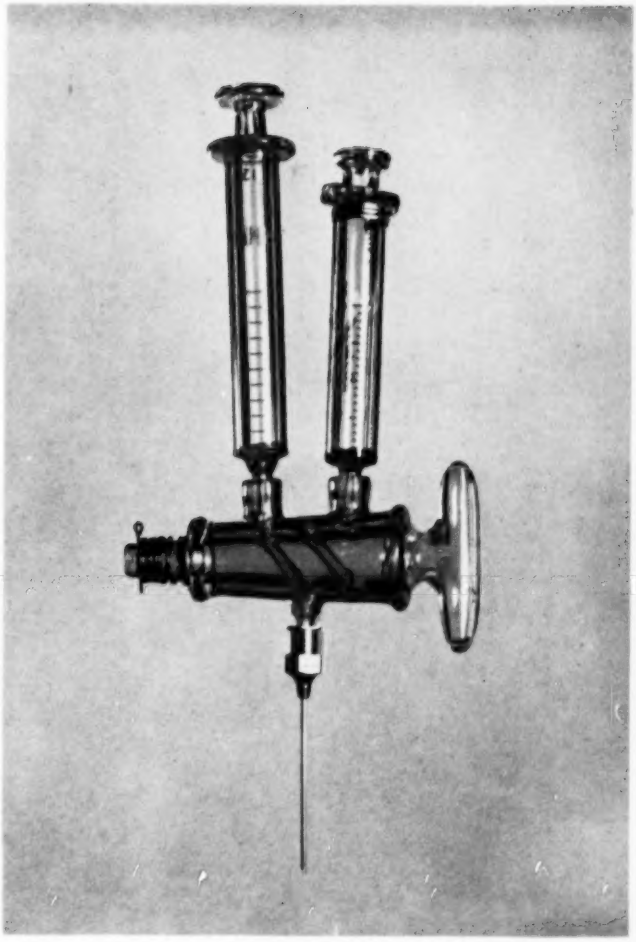

FIG. 2
Injection apparatus. For description see text.

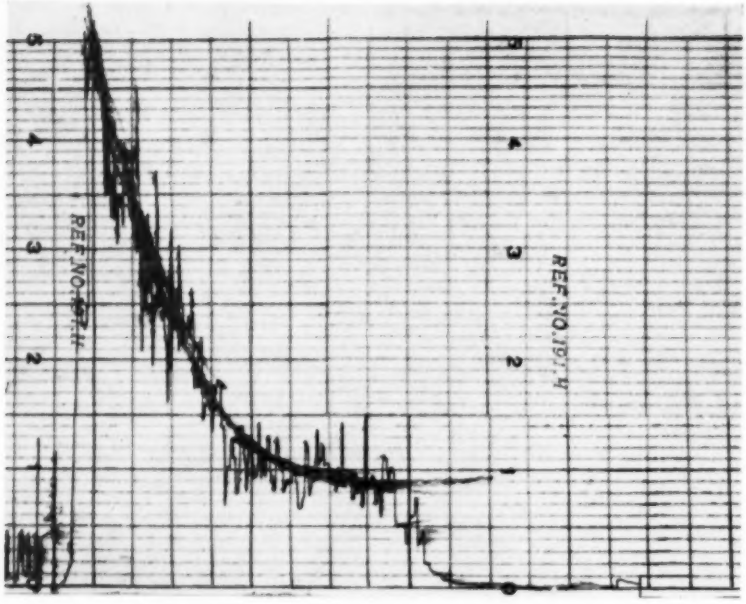

FIG. 3
Spurious curve due to intravenous injection.

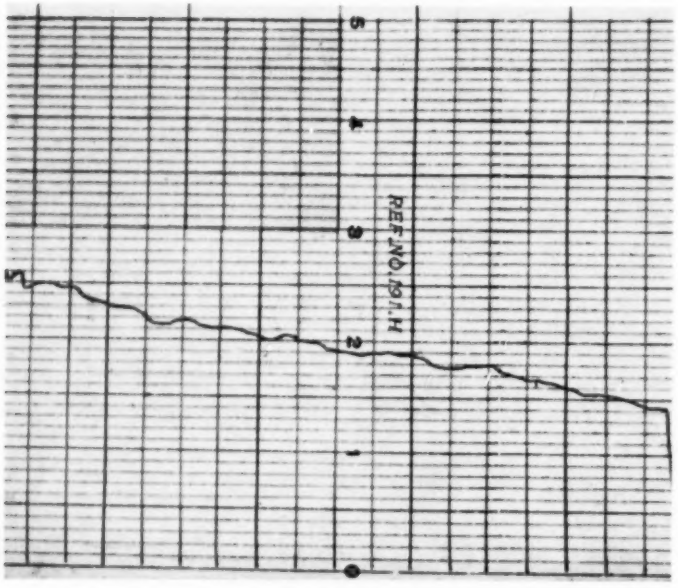

FIG. 4
Spurious curve due to intramuscular injection.

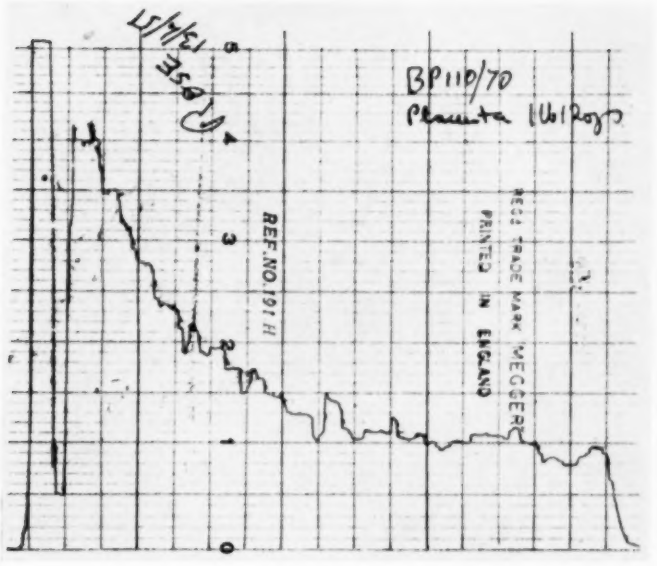

FIG. 5
Typical record from normotensive patient.

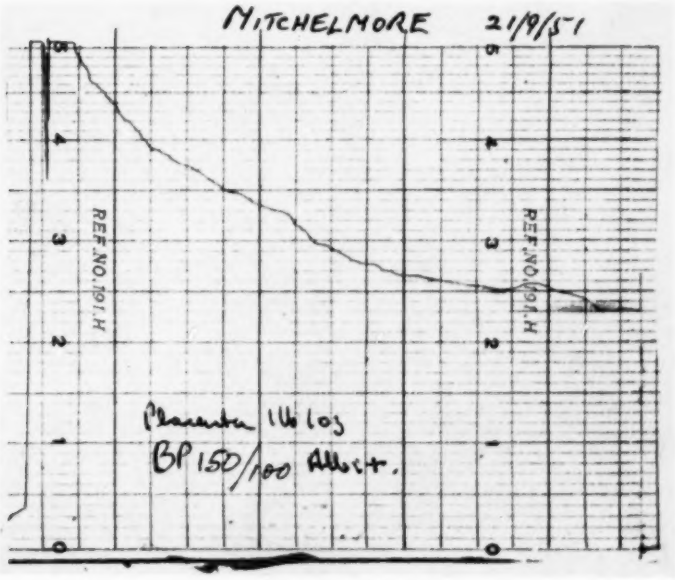

FIG. 6
Typical record in pre-eclampsia.

mA pen recorder. A record was thus obtained for some 3–5 minutes following the injection.

Even with such an apparently simple technique there were many failures, particularly if the foetus was at all active, usually due to the fact that during the changeover of syringes the point of the needle ceased to lie in the chorio-decidual space. To obviate this difficulty, the following apparatus was evolved (Fig. 2).

Two perfectly fitting 2-ml. all-glass syringes were attached to a ground-glass three-way tap, which in turn was attached to the needle. All joints were carefully tested to be sure that they were perfect. Into one syringe was drawn the solution of radio-active sodium, and into the other the solution of 2 per cent procaine. Using a fresh needle (therefore not contaminated with Na^{24}) the exploratory aspiration was made infiltrating with procaine as described above, and, when blood was obtained, the tap was turned so as to connect the saline syringe to the needle, when the injection was made fairly rapidly.

At the time of delivery, the weight of the placenta, freed from its membranes, was recorded.

Results

As has been indicated above, there were a number of failures, particularly in the earlier cases, which gave rise to two types of spurious recording. From 274 cases in which the placental site was located, blood-flow curves were obtained in 25, and of these, 10 were rejected because of faults in the technique or the apparatus. In one group of cases it was noted that blood could be withdrawn before the resistance of the uterine wall was encountered, and was assumed to come from a vein on the surface of the uterus. If the Na^{24} was injected into such a vessel, it was found to be carried away in a matter of a few seconds, resulting in a curve of the type shown in Fig. 3; or the Na^{24} would be found to have disappeared before the counter tube could be applied. Any curves of this type were therefore discarded on the assumption that the injection had missed the chorio-decidual space and entered a vein.

The other type of spurious curve obtained was characterized by a relatively long half-period of the order of 5–10 minutes as shown in Fig. 4. These curves were also more frequent in the earlier cases, and have been excluded on the assumption that in such cases the injection had been made into the uterine muscle, and that what in fact was being measured was the local tissue clearance of radioactive sodium as described by Kety (1948).

The remaining curves were of exponential form, as would be expected from Equation 2 above, typical records being presented in Figs. 5 and 6. A smooth curve was drawn from each record, as shown in Figs 7 and 8, and from these curves the half-period for the sodium disappearance was determined.

The data for the two groups of patients, normotensive and hypertensive, are presented in Table I, from which it is apparent that there is a marked difference in the half-period in the two groups, that for the hypertensive group being

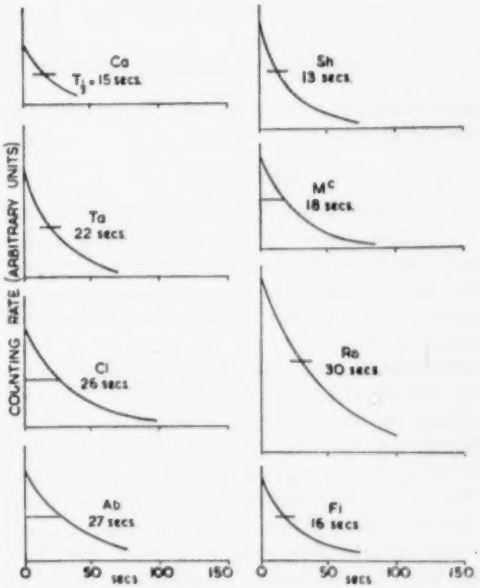

Fig. 7

Disappearance curve in normotensive patients.

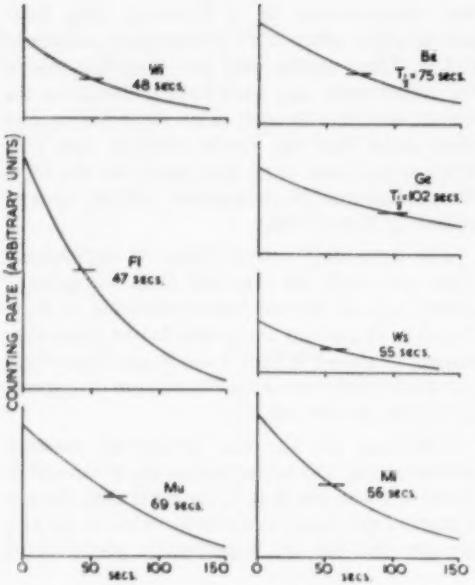

FIG. 8
Disappearance curve in hypertensive patients.

approximately 3 times as long as that for the normal group.

DISCUSSION

(A) *Interpretation of the Experimental Results*

(1) *Significance of the change in counting rate.* Perhaps the most important assumption that it is necessary to make in interpreting the above results is that the observed decrease in counting rate is due to the transport of Na^{24} away from the injection site by the blood stream. An alternative possibility is that the Na^{24} rapidly crosses the placental barrier to the foetal circulation, and that the reduction in the observed counting rate is due to the inverse-square law. The main evidence in support of the basic assumption depends on the fact that it is known, from considerable experience with the Na^{24} method for placental localization, that the counting rate over an anteriorly situated placenta following an intravenous injection of the isotope is approximately the same as that obtained over the praecordium. In a number of the patients reported on above, the curve was plotted until it reached the base line, which corresponded to the count rate to be expected form the same quantity of Na^{24} uniformly distributed over the whole circulatory system. At this stage the count rate over the heart was found to be approximately the same as that over the injection site, indicating that the major proportion of the isotope was in fact uniformly distributed throughout the maternal vascular system.

The above evidence can also be regarded as going a long way towards excluding the possibility that the observed changes in counting rate might have been due primarily to mixing in the placental pool. Finally, the exponential character of the curves obtained lends support to the belief that Equation 2 is in fact applicable to the data obtained, since either of the alternative possibilities discussed above would be expected to give curves which would depart considerably from the exponential form.

The Marginal Sinus. It follows from the above considerations that the pattern of maternal blood flow in the placenta is such that the test injection remains fairly well localized in a particular region, implying that each such region (presumably an individual cotyledon) has its own venous drainage system. Any lateral spread which does take place must occur in the two or three seconds occupied by the withdrawal of the needle and the positioning of the counter tube. Consequently these observations can be taken as evidence against the marginal sinus drainage mechanism postulated by Spanner (1935) and as supporting the conclusions of Bumm (1890), and of Hamilton and Boyd (1951).

In addition, it was often possible to form an idea of the position of the test site in relation to the placental margin by noting the depth of the chorio-decidual space when the needle was inserted. There was no noticeable correlation between the position of the test site and the observed disappearance rate, which correlation should have been quite marked if there were any appreciable radial component in the placental blood flow.

(2) *The disappearance curve, and its half-period.* An exponential curve can be character-

TABLE I

(*a*) *Normotensive Patients*

Patient	Half-period in seconds	Clinical details			
		Maturity—weeks	Placenta weight—g.	Blood-pressure	Urine
Ca	15	40	850	110/70	Normal
Ta	22	40	794	120/80	Normal
Cl	26	40	879	120/80	Normal
Ab	27	40	652	120/84	Normal
Sh	13	39	879	110/70	Normal
Mc	18	40	680	120/80	Normal
Ro	30	40	794	110/70	Normal
Fi	16	40	680	100/60	Normal

Mean half-period ... 21 seconds. Mean placental weight ... 776 g.

(*b*) *Hypertensive Patients*

Patient	Half-period in seconds	Clinical details
Wi	48	*Chr. Hypertension.* B.P.140/104. Alb. 20 mg. per cent. No oedema. Placental weight 652 g. Maturity 40 wks.
Fl	47	*Chr. Hypertension.* B.P. 140/100. Alb. 10 mg. per cent. No oedema. Placental weight 567 g. Maturity 39 wks.
Mu	69	*Chr. Hypertension.* B.P. 135/80. Alb. nil. No oedema. Placental weight 680 g. Maturity 39 wks.
Be	75	*Chr. Hypertension.* B.P. 140/80. Alb. nil. No oedema. Placental weight 397 g. Maturity 39 wks. Child weighed 3,450 g.
Ge	102	*Chr. Hypertension.* B.P. 140/80. Alb. nil. Slight oedema. Placental weight 567 g. Maturity 40 wks.
Ws	55	*Pre-eclamptic Toxaemia.* B.P. 140/95. Alb. 20 mg. per cent. Oedema +. No headache. Placental weight 595 g. Maturity 40 wks.
Mi	56	*Pre-eclamptic Toxaemia.* B.P. 150/100. Alb. 100 mg. per cent. Oedema +. No headache. Placental weight 482 g. Maturity 38 wks.

Mean half-period ... 65 seconds. Mean placental weight ... 563 g.

ized by its decay constant, in this case $\frac{v}{V}$ in Equation 2, or by the half-period, $T_{\frac{1}{2}}$. These two constants are related by the expression:

$$T_{\frac{1}{2}} = \frac{0.693\,V}{v} \qquad \text{.....(3)}$$

so that, other things being equal, the half-period is inversely proportional to the blood-flow rate v. On the other hand, it can also be seen from Equation 3 that the observed difference in half-period could, from the mathematical point of view, be equally well accounted for by differences in the placental pool volume V between the two groups of patients.

So far as we are aware, there is no evidence indicative of any appreciable difference between the volume of maternal blood contained in the placenta in normal and in hypertensive patients. Neither is there any significant difference in the weight of the delivered placentae in the two groups reported on above. Earn and Nicholson (1952) have reported appreciable distension of perfused placentae when the pressure of the perfusion fluid was increased, and it might be suggested that in hypertensive patients such a distension may occur. However, the placenta *in vivo* is in hydrostatic equilibrium with the amniotic fluid, and the latter is well known to be

in dynamic equilibrium so far as water and sodium are concerned, with the maternal blood plasma (Flexner and Gellhorn, 1942). Consequently it seems highly improbable that hypertension would in itself result in any appreciable distension of the maternal side of the placenta.

It is concluded, therefore, that the most reasonable and likely explanation for the difference in the half-period between the two groups of patients is that it represents a corresponding difference in the rate of placental blood flow.

(3) *Absolute determination of flow rate.* While we are mainly concerned with the relative placental blood flow in the two groups of patients, it is of interest to attempt to estimate the actual placental blood flow in a normal subject. However, this entails a knowledge of the placental pool volume V, and any estimate of this figure must necessarily be an approximation. From radiological evidence, and the examination of postmortem and Caesarean hysterectomy specimens, it would appear that 250 ml. would be a not unreasonable estimate. Substituting this figure, together with a half-period of 0.3 minutes, in Equation 3, indicates that the maternal placental blood flow in the normal subject near term is of the order of 600 ml./minute, i.e. about one-tenth of the total cardiac output (Hamilton, 1950).

Flexner and his co-workers (1948) have studied the transfer of Na^{24} from the maternal to the foetal circulation. From the data presented in their paper it is possible to estimate a lower limit for the maternal placental blood flow as follows: By extrapolation of the sodium transfer curve presented by Flexner *et al.* to term, a figure of about 9.5 mg. of Na/g. of placenta/hour is obtained. This is equivalent to the Na content of 3 ml. of plasma. Assuming a placental weight of 500 g. and a haematocrit of 40, it follows that at least 50 ml. of blood per minute are required to account for the observed transfer of Na^{24} to the foetus.

This figure however is a minimum estimate, being based on the assumption that the maternal plasma is completely cleared in its passage through the placenta, in that C_v in Equation 1 is equal to zero. However, our preliminary observations indicating that the arterio-venous difference, or the proportion of maternal plasma sodium cleared, was less than 10 per cent are supported by our observation that when Na^{24} is injected into the placental pool, most of the isotope is distributed through the maternal circulation instead of crossing the placental barrier. Consequently, it would appear that the assumption that about 7½ per cent of the sodium in the maternal plasma crosses the placental barrier as the blood passes through the placenta is a valid one. Hence the figures quoted above for the maternal placental blood flow can be regarded as being consistent with the data of Flexner and his associates for transfer of sodium across the placenta.

(B) *Clinical Significance*

Since Young (1914) first drew attention to the frequency of occurrence of the red infarct in the placentae of eclamptic women, the search for an aetiological factor in the placenta has gone on, and fresh impetus in this direction has been given by the recent work of Bastiaanse and Mastboom (1949) who were able to demonstrate hypertension occurring in the pregnant bitch when uterine ischaemia was produced by partial occlusion of the uterine arteries. That this hypertension did not occur in the non-pregnant bitch was taken as evidence that it was placental rather than uterine ischaemia which was to be incriminated.

This view was further strengthened by the discovery by Thompson and Tickner (1949) of a mono-amine oxidase in the placenta readily inactivated by decreased oxygen tension and therefore presumably by placental ischaemia, and there is much evidence in favour of its specific action being to destroy vaso-constrictor amines such as adrenaline. A deficiency of this enzyme in active form could therefore produce hypertension.

Against the placental ischaemia theory is the occurrence of postpartum eclampsia, when no placenta is present. The occurrence of eclampsia without hypertension is also suggestive of an extra-placental mechanism.

The results presented here are quite clear-cut, showing that, compared with the normal pregnant woman, the pre-eclamptic woman has a placental

ischaemia of the order of 60 per cent. That a similar ischaemia is found in the chronic hypertensive suggests that placental ischaemia is the result, and not the cause, of hypertension, though we can postulate an exacerbation of a pre-existing hypertension by placental ischaemia as an additional mechanism, which would account for the known tendency of the chronic hypertensive to develop a superimposed pre-eclampsia.

In all the cases presented the child was delivered alive. The healthy placenta must therefore, like the kidneys, have a safety margin of supply over demand of more than 50 per cent, and in pre-eclampsia and chronic hypertension this safety margin must be seriously reduced.

Summary and Conclusions

In an attempt to study the role of placental ischaemia in the aetiology of pre-eclampsia, the relative rates of maternal blood flow in the placentae of normal, pre-eclamptic, and chronic hypertensive women have been determined.

The normal maternal placental blood flow between 38 weeks and term is of the order of 600 ml./min., and in pre-eclampsia and chronic hypertension there is a reduction to about one-third of this figure.

Because this reduction occurs in chronic hypertensive as well as pre-eclamptic women, it is suggested that the origin of the hypertension is extra-placental, though this does not exclude a further rise due to placental ischaemia.

The healthy placenta has a functional safety margin of over 50 per cent. It is also inferred that the marginal sinus does not function as a distal collecting vein for the maternal blood leaving the placenta, each cotyledon having probably its own arterial supply and venous drainage.

Part of the work reported here was done with the assistance of a Leverhulme Grant from the Royal College of Obstetricians and Gynaecologists. This assistance is gratefully acknowledged.

We are also indebted to the Nursing Staff of the Ante-natal Ward at Hammersmith Hospital for their great assistance.

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PLACENTAL POLYSACCHARIDE AND THE AETIOLOGY OF THE TOXAEMIA OF PREGNANCY

BY

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THE present study has its origin in our experience that in eclampsia and abruptio placentae such changes as bleeding (capillary in particular), tissue oedema and fibrinoid degeneration of the vessel walls were observed not only in the uterine wall but also in such other organs as the liver, brain and kidney. These changes suggested an allergic factor. Much work has actually been done on the allergic aetiology of the condition, but little attention has been given to serology.

Our first efforts were devoted to finding a responsible allergen. It was clear that foetal elements have nothing to do with the allergen as a hydatid mole frequently causes a toxaemia. The placenta was thus first brought under suspicion. The protein of the placenta was, however, discarded, as it is unusual for a protein to be auto-antigenic. My colleague, Nagai, and myself first studied, therefore, the role of placental lipids but only to discard them, as no anti-lipid antibody was found in the serum of toxaemia patients.

Finally, the polysaccharide of placenta attracted our attention, because an experimental nephritis caused by pneumococcal polysaccharide (Suzuki) had much the same appearance as the pathological changes in the kidney in toxaemia.

EXTRACTION OF HUMAN PLACENTAL POLYSACCHARIDE SUBSTANCE

After a series of investigations the procedure as shown in Table I was found to be the best for the extraction of placental polysaccharide.

CHEMICAL PROPERTIES OF HUMAN PLACENTAL POLYSACCHARIDE

The polysaccharide is a white amorphous powder. It is soluble in water, but not soluble in alcohol and ether. It is non-dialytic. A 1 per cent solution of the polysaccharide is light yellow in colour. The antigenic power of the solution is not diminished by heating for an hour at 100°C. It gives a strongly positive Molish's reaction. The B-fraction of the polysaccharide as seen in Table I gives a negative reaction with trichloracetic, sulphosalicylic acid, the Biuret and Millon's tests, picric acid, xanthoprotein, and iodine. The A-fraction is, however, positive to the Biuret xanthoprotein, and picric acid tests. When tested by means of Hagedorn-Jensen's method after hydrolysis with HCl, it contained about 80 per cent reductive sugar. Nitrogen was from a trace to 1 per cent and from 8 to 12 per cent in B and A fractions respectively.

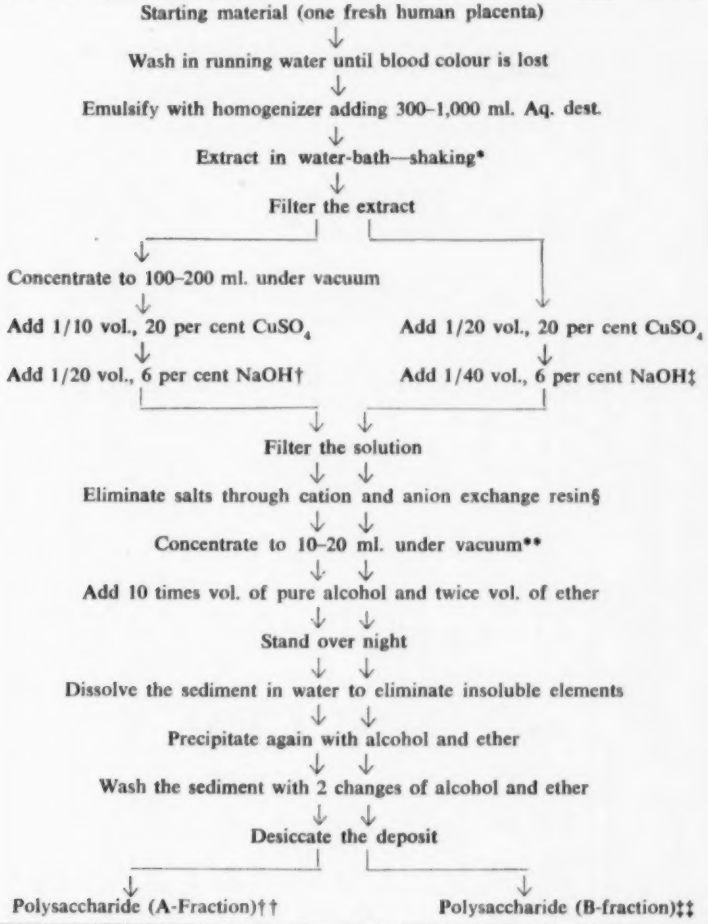
SEROLOGY OF THE POLYSACCHARIDE

(*a*) *Antigenic property.* In the first experiment 11 rabbits were injected with 0.5 ml. emulsion of human placenta intravenously along with 10 ml. of the same emulsion administered intraperitoneally, twice a week, for 10 weeks. The blood was taken from the animals 3–7 days after the last injection and was examined for precipitation reaction. In 10 out of the 11 cases, the precipitation titre against placental emulsion was 10 to 80, and in the last case it was 200 against human polysaccharide.

In the second experiment 2 ml. supernatant fluid of a heated extract of placenta was injected

TABLE I

Procedure of polysaccharide extraction from human placenta


Starting material (one fresh human placenta)
Wash in running water until blood colour is lost
Emulsify with homogenizer adding 300–1,000 ml. Aq. dest.
Extract in water-bath—shaking*
Filter the extract
Concentrate to 100–200 ml. under vacuum
Add 1/10 vol., 20 per cent $CuSO_4$
Add 1/20 vol., 6 per cent NaOH†
Add 1/20 vol., 20 per cent $CuSO_4$
Add 1/40 vol., 6 per cent NaOH‡
Filter the solution
Eliminate salts through cation and anion exchange resin§
Concentrate to 10–20 ml. under vacuum**
Add 10 times vol. of pure alcohol and twice vol. of ether
Stand over night
Dissolve the sediment in water to eliminate insoluble elements
Precipitate again with alcohol and ether
Wash the sediment with 2 changes of alcohol and ether
Desiccate the deposit
Polysaccharide (A-Fraction)††
Polysaccharide (B-fraction)‡‡

Precautions:

* Shake the emulsion in water-bath till water boils. The shaking should be continued till the water cools down again.

† Six per cent sodium hydroxide is added to eliminate protein. Sodium hydroxide solution should be added till the filtrate becomes negative to sulphosalicylic acid reaction.

‡ Sodium hydroxide solution should be added till the filtrate becomes negative for Biuret reaction.

§ Amberlite I R 120 and I RA 410 should be used. As the activators 1.5N–HCl and 1.5N–NaOH should be used for cation and anion exchange resin respectively.

** Before the concentration, pH should be corrected to 7.0. After the concentration, pH should be corrected to 7.0–7.4.

†† 50 to 100 mg. will be obtained from one placenta. This fraction is positive for Biuret reaction.

‡‡ 20 to 30 mg. will be obtained from one human placenta. This fraction gives a negative or trace reaction in the Biuret test.

TABLE II

Precipitin reaction and complement fixation reaction of rabbit serum immunized with human placental polysaccharide

Antigen: Human placental polysaccharide

Rabbit No.	Precipitin reaction						Complement fixation reaction							
	Dilution of antigen						Unit of complement							
	100	200	400	800	Saline	Precipitin titre	2	4	6	8	10	12	Control	Complement fixing titre
36	−	−	−	−	−	0	−	+	++	+++	+++	+++	+++	2
37	+	+	−	−	−	200	−	−	−	+++	+++	+++	+++	6
38	+	−	−	−	−	100	−	−	−	+	++	+++	+++	6
39	+	+	−	−	−	200	−	−	−	+	++	+++	+++	6
40	+	+	+	−	−	400	−	++	+++	+++	+++	+++	+++	2
41	−	−	−	−	−	0	−	−	+++	+++	+++	+++	+++	4
42	−	−	−	−	−	0	−	−	++	+++	+++	+++	+++	4
43	+	+	−	−	−	200	−	−	−	−	−	++	+++	10
44	−	−	−	−	−	0	−	−	−	−	−	+	+++	10
45	++	+	+	−	−	400	−	−	−	−	−	++	+++	10
46	+	−	−	−	−	100	−	−	−	−	−	+	+++	10
47	+	−	−	−	−	100	−	−	−	−	−	+	+++	10
48	+	+	−	−	−	200	−	−	−	−	++	+++	+++	8
49	−	−	−	−	−	0	−	−	−	−	++	+++	+++	8
50	+	−	−	−	−	100	−	−	−	−	−	+++	+++	10
51	+	−	−	−	−	100	−	−	++	+++	+++	+++	+++	4
52	−	−	−	−	−	0	−	−	−	++	+++	+++	+++	6
Control 5	−	−	−	−	−	0	+++	+++	+++	+++	+++	+++	+++	0

In precipitin reaction:

− No precipitation. + Positive but slight precipitation. ++ Definite precipitation.

In complement fixation reaction:

− No haemolysis. + Slight haemolysis. ++ Moderate haemolysis. +++ Complete haemolysis.

TABLE III

Precipitin reaction and complement fixation reaction of rabbit serum immunized with rabbit placental polysaccharide.

Antigen: Rabbit placental polysaccharide.

Rabbit No.	Precipitin reaction								Complement fixation reaction						
	Dilution of antigen								Unit of complement						
	100	200	400	600	800	1600	Saline	Precipitin titre	2	4	6	8	10	Control	Complement fixing titre
6									−	−	++	+++	+++	+++	4
7									−	−	+	+++	+++	+++	4
8									−	−	−	++	+++	+++	6
9	+	+	+	+	+	−	−	800	−	−	−	++	+++	+++	6
10	+	+	+	+	+	−	−	800	−	−	−	+	++	+++	6
11	+	+	+	−	−	−	−	400	−	−	−	++	+++	+++	6
12	+	+	−	−	−	−	−	200	−	−	+	++	+++	+++	4
13	−	−	−	−	−	−	−	0	+++	+++	+++	+++	+++	+++	0
14	−	−	−	−	−	−	−	0	+++	+++	+++	+++	+++	+++	0
Control 4	−	−	−	−	−	−	−	0	+++	+++	+++	+++	+++	+++	0
Control 5	−	−	−	−	−	−	−	0	+++	+++	+++	+++	+++	+++	0

In precipitin reaction:

− No precipitation. + Positive but slight precipitation.

In complement fixation reaction:

− No haemolysis. + Slight haemolysis. ++ Moderate haemolysis. +++ Complete haemolysis.

into 12 rabbits intravenously at 2–3 days' interval for 11–22 times. In 9 out of the 12 cases, the sera had a precipitation titre of 10–80 against placental emulsion. In the remaining 5 cases, the titre was 100–800 against the polysaccharide.

In the last experiment 47 rabbits were injected with 1–10 mg. of human placental polysaccharide in saline solution. The injection was repeated every day or every other day for 7 to 30 times (1 mg. × 20–30, 5 mg. × 15–20, and 10 mg. × 7–10), and the blood was taken 3–7 days after the last injection.

As summarized in Table II, the precipitation titre of the sera against human placental polysaccharide was 100–1,200 in 28 out of the 47 rabbits. The complement fixation reaction, using the polysaccharide as the antigen, was positive in all cases (2 to 8 units of the complement were fixed). The sera reacted with the polysaccharide exclusively. They showed no reaction with human serum, placental protein, lipid and phosphatid, and Boivin fraction from placenta.

The results of these three experiments indicate that the polysaccharide has an antigenic property.

(*b*) *Human placental polysaccharide as an anaphylactic antigen.* Eight guinea pigs (200–300 g.) were sensitized with the polysaccharide injected in a dosage of 10 mg. intraperitoneally every day for 5–20 days. Two to 3 weeks later 20–40 mg. of the polysaccharide were re-injected intravenously in these sensitized animals. In 2 out of the 8 animals such typical anaphylactic signs as temperature fall, unrest, fluffing up of hairs, chill and incontinence, appeared after the re-injection. In 2 other animals a considerable lowering of the temperature and some other anaphylactic signs resulted. A single intravenous injection of the polysaccharide did not cause any of such symptoms.

(*c*) *Schultz-Dale test.* Fifteen guinea pigs were sensitized as in experiment (*b*). Two to 3 weeks later, the uterus and a tip of ileum were removed, each as a piece of 0.5 inch long. They were measured for their movement by Magnus's method in Tyrode's solution. In 10 out of the 15 cases a prompt increase in contraction was brought about, as shown in Fig. 1, when 10–30 mg. of the polysaccharide were added to the medium. In none of the control materials was such an increase in contraction observed.

(*d*) *Homoio-antigenicity of rabbit placental polysaccharide.* In the first experiment 6 rabbits were immunized with a heated extract of rabbit placenta as in the second experiment of item (*a*). The blood was taken 3–7 days after the last injection and was examined for antibody against rabbit placental polysaccharide, which had been extracted from rabbit placenta in a manner similar to that in the case of human placenta. The complement fixation reaction was positive in all cases; 6–10 units of complement were fixed. No reaction occurred, however, when rabbit serum, saline or heated extract of rabbit placenta, and phosphatid of rabbit placenta were used as the antigen.

In the second experiment 9 rabbits were immunized with rabbit placental polysaccharide as in the last experiment of item (*a*). The precipitation titre of these rabbit sera for rabbit placental polysaccharide was 200–800. A complement fixation test, with rabbit placental polysaccharide as the antigen, was positive in 7 of the 9 cases, and 4–6 units of complement were fixed.

There remains no doubt that the rabbit placental polysaccharide by itself is capable of developing precipitation and complement fixing antibody in the same species of animals, e.g., the rabbit placental polysaccharide must be homoio-antigenic.

(*e*) *Relationship between human and rabbit placental polysaccharide.* Our experiment indicated that : (1) sera of rabbits immunized with human placental polysaccharide reacted with rabbit placental polysaccharide almost to the same extent as they did with human placental polysaccharide. (2) Sera of rabbits immunized with heated extract of rabbit placenta reacted with human placental polysaccharide as they did with rabbit placental polysaccharide. (3) Three guinea pigs were passively sensitized by a transfusion of a serum of rabbits sensitized with rabbit placental polysaccharide. Twenty-four hours later 20 mg. human placental polysaccharide were injected intravenously as a reacting antigen. In 2 of the 3 cases a temperature fall and other anaphylactic symptoms were brought

about. And (4) intestine and uterus of 3 guinea pigs passively sensitized as above with rabbit placental polysaccharide were tested for the Schlutz-Dale reaction. In 2 of the 3 cases the test was positive for human placental polysaccharide.

Human placental polysaccharide and rabbit placental polysaccharide must have factors common in regard to their serological property. In all probability, therefore, human placental polysaccharide can be considered as homoioantigenic as is the rabbit placental polysaccharide.

Serology of Toxaemia of Pregnancy

It must be of the greatest importance here to study whether in sera of toxaemia patients antibodies against placental polysaccharide could be found or not.

(1) *Precipitin reaction.* Sera from 119 cases of toxaemia were tested for the precipitin reaction against human placental polysaccharide. In 20 of the 119 cases, or in 17 per cent, the precipitin titre was between 100 and 800. In control examination of 39 normally pregnant women, the reaction was negative in all cases except in 1 case which showed a titre of 200. A negative result was invariably obtained in 32 non-pregnant control cases.

(2) *Complement fixation reaction.* Sera from 142 cases of toxaemia were examined for complement fixation. In 30 of the 142 cases, or in 21 per cent, the reaction was positive (2 to 8 units of fixation complement). In 81 control cases of normal pregnancy only 2 cases showed a positive reaction (2 units fixation). In these experiments only the sera which had been proved to be negative for the Wassermann and cardiolipin reaction were utilized.

In 112 of the toxaemia cases, both precipitin and complement fixation tests were employed together. In 38 of the 112 cases, or in 34 per cent, at least 1 of these reactions was proved to be positive. In a series, in which the B-fraction or Biuret negative fraction of the polysaccharide (see Table I) was used as the antigen, the reaction was positive in 5 out of the 11 cases or in 45 per cent.

Table IV

Complement fixation reaction of toxaemia sera against human placental polysaccharide

	Diagnosis	Number of cases	Number of positive cases
Toxaemia of pregnancy	Oedema of pregnancy ...	11	2
	Kidney of pregnancy (slight)	36	8
	Kidney of pregnancy (severe)	62	12
	Pre-eclampsia	20	4
	Eclampsia	11	2
	Abruptio placentae	2	2
	Total	142	30 (21.1 per cent)
Control	Normal pregnancy	81	2
	Non-pregnant women ...	23	0
	Normal men	16	0
	Syphilis	16	0
	Cancer of uterus	69	0
	Total	205	2

Details of positive cases

	Complement fixing titre	Number of cases
Toxaemia of pregnancy ...	2	15
	4	2
	6	11
	8	2
Normal pregnant women ...	2	2

(3) *Anaphylactic reaction.* Toxaemia serum (3 ml.) was injected into 4 guinea pigs intraperitoneally to cause a possible passive anaphylaxis. Twenty-four to 48 hours later, 20 to 30 mg. human placental polysaccharide were injected into the animals intravenously. In one of the 4 animals a temperature fall and other slight anaphylactic symptoms were brought about.

(4) *Schultz-Dale test.* Guinea pigs were passively sensitized as in item (3), and the uteri and intestines of the animals were tested for the Schultz-Dale reaction. The reaction was positive in 9 of 18 cases examined, or in 50 per cent. An example of the positive reaction is shown in Fig. 2. In 2 of 7 cases tested during a normal pregnancy the reaction was also positive. In none of the non-pregnant control cases, however, was the reaction positive.

(5) *Antibody against the polysaccharide in gamma-globulin.* Gamma-globulin was isolated from toxaemia sera by means of an ethanol precipation method. The gamma-globulin reacted with human placental polysaccharide, and a complement fixation test was positive in 8 of 27 examined cases. The role of gamma-globulin as a carrier of antibody against the polysaccharide was also investigated by the Schultz-Dale test with a positive result in 8 of 17 examined cases.

Pathology of Experimental Toxaemia caused by Placental Polysaccharide

In 24 cases of toxaemia, an autopsy was performed and pathological changes in the liver, kidney and heart were studied.

Then, in rabbits in various conditions, human polysaccharide was administered through a number of routes. The rabbits were examined for pathological changes in such organs as the liver, kidney and heart, and the changes were comparatively studied with those in human toxaemia cases.

(1) *Pathology of toxaemia.* Pathological changes in the liver, kidney and heart of toxaemia patients were much the same as those already reported by many workers. Detailed description of them will be, therefore, left out here.

(2) *Rabbits used.* (i) Non-pregnant, (ii) pseudo-pregnant, (iii) pregnant, and (iv) rabbits sensitized with human placental polysaccharide were used. For the purpose of sensitization 5 or 10 mg. of human placental polysaccharide were administered intravenously every day or every other day for 20 or 10 times respectively.

(3) *Route of the polysaccharide administration as reacting agent.* The polysaccharide as a reacting agent was administered through the following routes: (i) 100 mg. in the hepatic artery, (ii) 200 mg. in the portal vein, (iii) 20–30 mg. in the renal artery, and (iv) 70–300 mg. in the vein of the ear. The animals were killed 1–3 days after the injection and pathological examination was made of the organs mentioned above.

(4) *Results*: (i) *Liver.* The liver of pregnant and sensitized rabbits looked either anaemic or haemorrhagic after a hepatic arterial administration of human placental polysaccharide. In the cut surface, which looked swollen, there appeared necrotic lesions. Microscopically, the lesions were sharply defined. In a case of the pregnant rabbit, the necrosis spread to the whole lobule, and was accompanied by a congestion and haemorrhage.

In the non-necrotic portion of the lobules, there were cloudy swelling and vacuolar or fatty degeneration of the liver tissue. In some Glisson's capsules, there were haemorrhage, infiltration of round and white cells, perivascular oedema, fibrinous thrombus in the branch of the portal vein, and fibrinoid degeneration of the vessel wall. The changes in sensitized rabbits were apt to be milder than the pregnant ones.

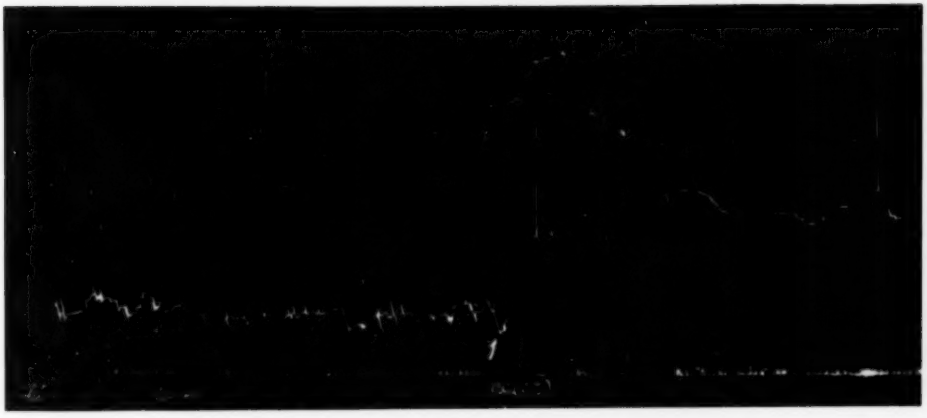
In pseudo-pregnant cases, degenerative changes were predominant without being accompanied by a necrosis. There were only slight degenerative changes in non-pregnant rabbits.

The liver changes caused by a portal administration of human placental polysaccharide were much the same as those mentioned above, though they were apt to be a little milder. The changes were most pronounced in pregnant animals, a little slighter in sensitized animals, and minimal in pseudo- and non-pregnant animals.

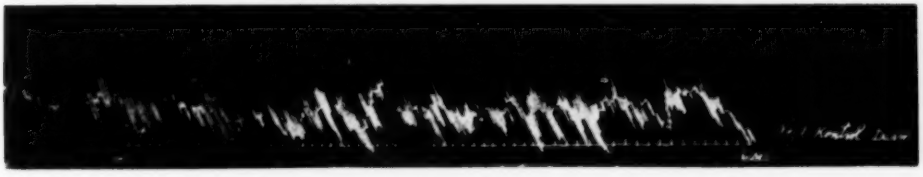
When human placental polysaccharide was administered through the ear vein, slight but similar changes were brought about in pregnant and sensitized rabbits only when a great dosage (300 mg.) was used.

(ii) *Kidney.* After the administration of human placental polysaccharide into the renal artery of pregnant rabbits, there were few changes in the glomeruli. In the tubules, however, there were slight granular and fatty degeneration in the epithelium, and the lumina of the tubules were filled with a coagulum of protein and hyaline casts. In non-pregnant rabbits there were almost no changes in the kidney.

It was interesting to note that, in pregnant and sensitized rabbits, there occurred remarkable changes in the glomeruli when the polysaccharide was introduced into the hepatic artery or portal vein. The changes were: swelling of the glomeruli and the wall of the capillary loops, anaemia or congestion of the glomeruli, cloudy

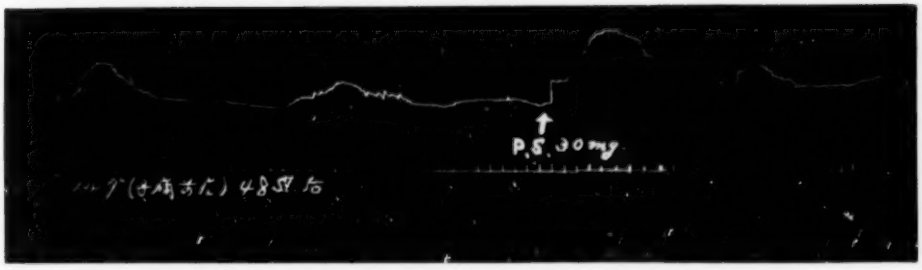


(*a*) Guinea pig sensitized with human placental polysaccharide.
Arrow indicates the time of addition of the polysaccharide.

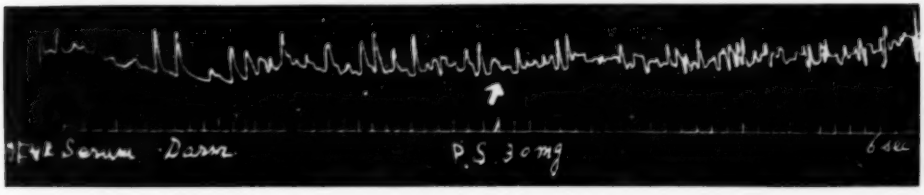


(*b*) Control.

FIG. 1
Schultz-Dale test with intestine of guinea pig.



(*a*) Guinea pig sensitized with human toxaemia serum.
Arrow indicates the time of addition of human placental polysaccharide.



(*b*) Control.

FIG. 2
Schultz-Dale test with intestine of guinea pig.

M.K.

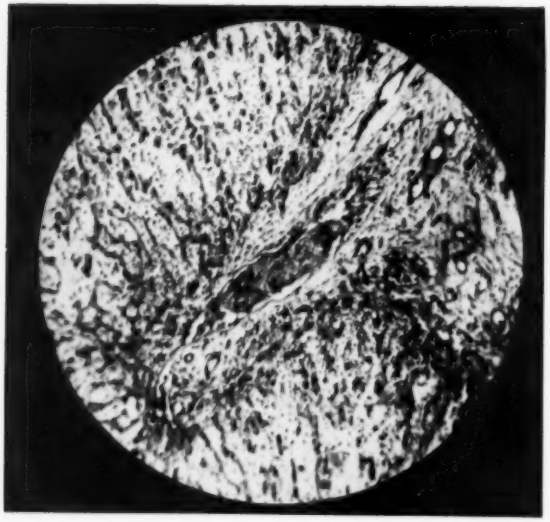


FIG. 3

Biopsy finding in liver of pregnant rabbit after injection of human placental polysaccharide (100 mg.) into hepatic artery. Fibrinous thrombi in the branches of the portal vein, oedematous swelling, haemorrhage in the Glisson's capsule and necrosis of liver cells are seen. × 50

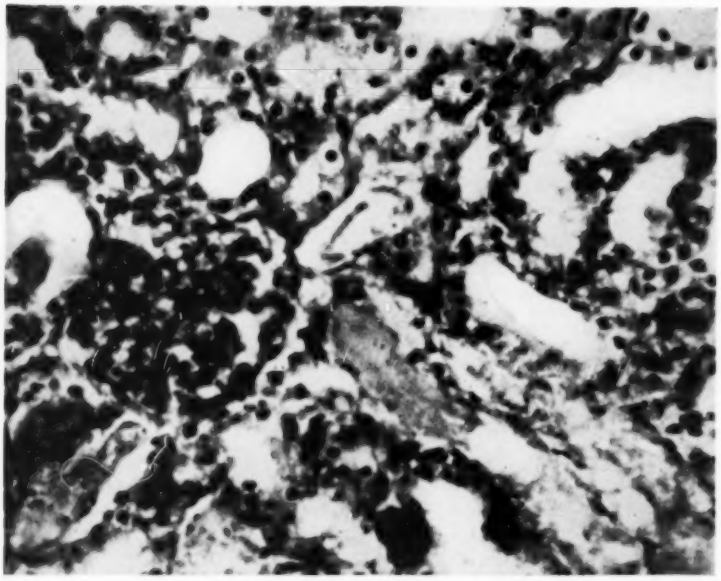


FIG. 4

Biopsy finding in kidney of pregnant rabbit after injection of human placental polysaccharide (20 mg.) into renal artery.
Increase in leucocytes in glomeruli, cloudy swelling of epithelium of tubules, epithelium partially necrotic. The lumina of the tubules contain protein and hyaline casts. × 320

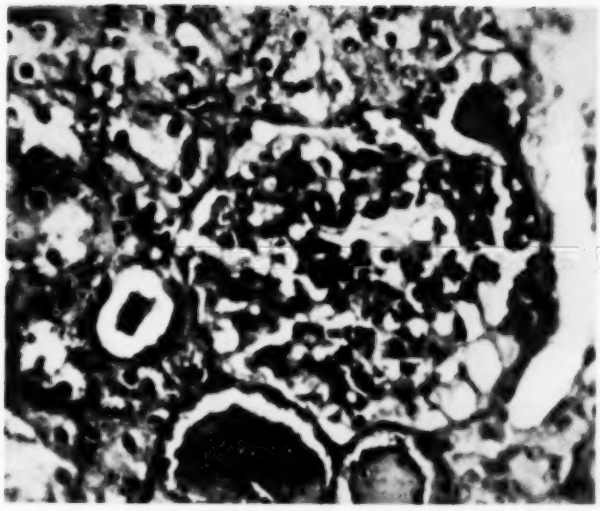


FIG. 5

Biopsy finding in sensitized rabbit kidney after reinjection in the vein of ear.

Sensitizing antigen: human placental polysaccharide.
Reacting antigen: human placental polysaccharide (300 mg.).
Haemorrhage and exudation of proteinoid substance in the Bowman's capsule are seen. ×320

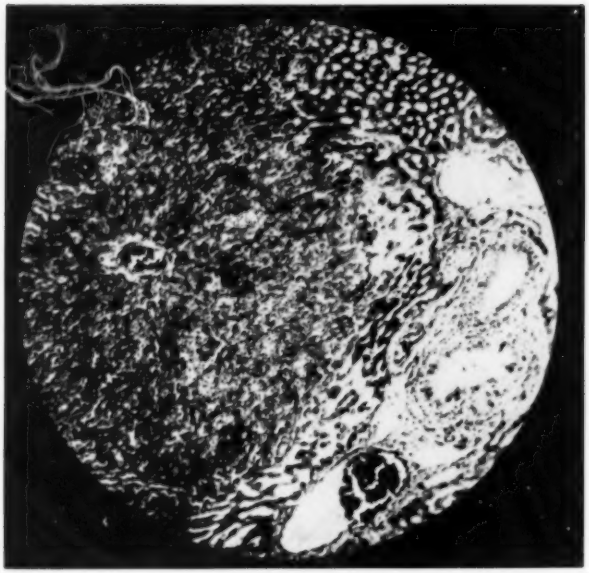


FIG. 6

Biopsy finding in liver of sensitized rabbit after reinjection into hepatic artery.

Sensitizing antigen: rabbit placental polysaccharide.
Reacting antigen: rabbit placental polysaccharide (200 mg.).
Necrosis is seen. × 50

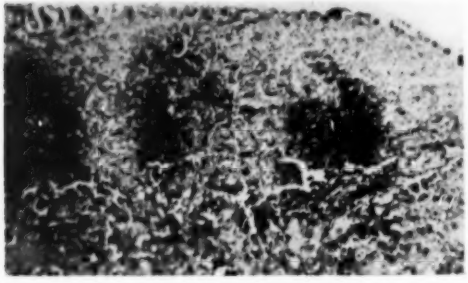


FIG. 7

Biopsy finding in liver of pregnant rabbit with hypertension after injection of human placental polysaccharide (100 mg.) in hepatic artery.

Hypertension was brought about experimentally, prior to pregnancy, by cutting n. depressor. Fibrin exudation in necrotic lesion is seen. (Fibrin staining.) × 50

swelling of the epithelium, enlargement of the lumina, and degenerative changes in the epithelium of the tubules. These changes corresponded to those found in cases of glomerulonephrosis. Slight but similar changes were brought about even in non-pregnant animals.

When human placental polysaccharide in large dosage was administered into the ear vein, slight changes of a similar nature were brought about in pregnant and sensitized rabbits. No change was brought about, however, in non-pregnant animals.

The pathological changes in such organs as the lung, heart, brain, uterus, placenta and endocrine gland were also examined in these series of rabbits.

(5) *Experiments with rabbit placental polysaccharide.* A series of experiments similar to those in (2) to (4) was designed and performed using rabbit placental polysaccharide as sensitizing and reacting agent and similar results were obtained.

One thing calls for consideration. Although these pathological changes in experimental animals were similar to those of toxaemia patients, they were not quite the same. Slow but steady action of the sensitizing and reacting agent in human cases and concentrated and sudden action of them in experimental animals may be one of the causes of the difference in appearance. On the other hand, however, such factors as a "disposition" or "predisposing factor" may play a role in actual toxaemia patients, as the disease occurs only in a small proportion of pregnant women. The problem was then studied as follows.

(6) *Experiments in rabbits experimentally made hypertensive.* In view of the fact that hypertensive persons are more apt to suffer from toxaemia, experiments as described in (2) to (4) were carried out in rabbits which had been made hypertensive experimentally. An experimental hypertension was brought about by the Koch and Braecker's method of bilateral blocking of the blood-pressure controlling nerves.

When administered into the ear vein, human placental polysaccharide as already described did not cause severe liver changes in normal pregnant rabbits unless a greater dosage than 300 mg. was used. However, an administration of 110 mg. of the polysaccharide into the ear vein resulted in a severe necrosis of liver accompanied with a haemorrhage in pregnant rabbits which had been made hypertensive experimentally.

Changes in the kidney were also more pronounced in the latter than in the former.

(7) *Loading test with common salt.* In the next series of experiments, an excess of common salt was given to the rabbits. The results were, however, not sufficiently uniform to justify any conclusion. Nevertheless, the following series of rabbits was interesting. In this series, 5 ml./kg. of 10 per cent saline was injected intravenously every day for 3 days after an injection of 30 mg. of the polysaccharide into the renal artery. In 1 of the rabbits which had been sensitized with the polysaccharide, renal changes similar to those found in human toxaemia were present.

Summary and Conclusions

(1) We isolated polysaccharide substance from human and rabbit placenta.

(2) The human placental polysaccharide has an antigenic property *in vitro* and *in vivo.*

(3) The rabbit placental polysaccharide was proved to have a homoio-antigenicity.

(4) The human and rabbit placental polysaccharides have some common antigenic properties. Therefore, the human placental polysaccharide can be considered to have an auto-antigenicity.

(5) Antibodies against human placental polysaccharide can frequently be found in the serum of toxaemia patients while it can only seldom be found in normal pregnancy. It is thus possible that the polysaccharide may play a role in the aetiology of toxaemia.

(6) In various organs of toxaemia patients morbid changes corresponding to those of an allergic nature can be found.

(7) When placental polysaccharide is injected into pregnant rabbits or rabbits which have been sensitized with the polysaccharide, morbid changes, which are similar to those of toxaemia patients, are brought about; while minimal or no changes are found in normal rabbits.

(8) In hypertensive rabbits human placental

polysaccharide causes more severe changes than in non-hypertensive ones.

(9) An excess of common salt as a predisposing agent in toxaemia seems to be worthy of further investigation.

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GLOMERULAR FILTRATION RATE AND RENAL BLOOD FLOW IN HYPERTENSIVE TOXAEMIA OF PREGNANCY*

BY

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THE role of the kidney has always been thought to be important for the development of the syndrome " toxaemia of pregnancy ". A change in renal function pathognomonic for toxaemia of pregnancy has, however, not been demonstrated. Several investigators using clearance techniques have studied in detail the changes in renal function during toxaemia. Among others the investigations by Chesley *et al.* (1940), Corcoran and Page (1941), Dill *et al.* (1942), Wellen, Welsh and Taylor (1942), Kenney, Lawrence and Miller (1950) may be mentioned. The findings have not been consistent, partly due to the fact that the importance of the stage of pregnancy, at which the study was made, has not been duly considered. All earlier authors have thought that the renal clearances are unaltered during pregnancy, but, as shown by Bucht (1951), the renal plasma flow (calculated from the PAH-clearance) as well as the glomerular filtration rate (inulin clearance) undergoes typical changes during pregnancy (Table I). Earlier results during toxaemia have been variable both regarding the inulin clearance and the diodrast clearance. All workers agree that the inulin clearance is lowered during toxaemia, while most investigators have found a normal diodrast clearance with the exception of Kenney, who found the clearance of diodrast to be considerably lower in toxaemia than during normal pregnancy.

The present study was undertaken in order to enlarge the range of toxaemias studied with clearance techniques and compare the values found with those obtained in normal pregnancy in the same month of gestation (Bucht, 1951).

MATERIAL AND METHODS

Twenty-nine patients with toxaemia of pregnancy were studied. None had renal disease or toxemia of pregnancy earlier. The highest blood-pressure reading during ambulant examination accepted as normal was 145/95 mm.Hg. All patients except 2 (Nos. 17 and 19) had normal blood-pressure at examination 4–24 months after the toxaemic pregnancy. All patients were free of proteinuria at follow-up examination, but in some cases the proteinuria lasted for more than 4 months after delivery. All patients had normal urine analysis at the follow-up examination.

All patients had elevated blood-pressure, systolic and diastolic, proteinuria and varying oedema as signs of toxaemia. They were admitted to the hospital shortly after the start of the symptoms and investigated within the first 48 hours in the hospital—in the 26th to 44th weeks of pregnancy. Table II outlines the clinical picture. No attempt has been made to group the material according to the severity of the disease in view of the difficulty in finding objective evidence. Only one case in the present series had eclampsia with one seizure after delivery. The lack of more cases of eclampsia is partly due to the effectiveness of the prenatal care.

The results in the cases of toxaemia have been compared with the finding in a comparable material of pregnant and non-pregnant women in the same age-groups.

All cases were studied again after a follow-up period of 4–24 months.

All patients were studied in the morning in the fasting state; 1–2 hours before the examination 1 litre of plain water and, in some cases, 3–6 g. creatinine were given by mouth. Inulin clearance was determined after an intravenous injection of about 100 ml. inulin, given about 1 hour

* Aided by grants from the Knut and Alice Wallenberg Foundation and from the Andersson Foundation.

TABLE I

Renal function in normal pregnancy (Bucht, 1951)

	Normal subjects, female			Normal pregnancy, 2 to 8 months			Normal pregnancy, 9 to 10 months		
	No. of subjects	Average	δ	No. of subjects	Average	δ	No. of subjects	Average	δ
Inulin clearance/1.73m²	23	122 ± 5.1	24.3	17	170 ± 5.6	23.2	10	156 ± 9.6	30.5
PAH clearance/1.73m²	23	557 ± 29.7	142.6	19	800 ± 34.7	151.3	13	571 ± 24.7	89.0
Ex. creatinine clearance/1.73m²	22	148 ± 4.5	250	19	186 ± 11.8	565	13	153 ± 6.53	236
$\frac{\text{Inulin clearance} \times 100}{\text{PAH-clearance}}$	23	22.7 ± 1.0	4.8	17	22.1 ± 1.26	5.18	10	28.9 ± 1.24	3.93
$\frac{\text{Ex. creatinine clearance}}{\text{Inulin clearance}}$	23	1.25 ± 0.03	0.16	17	1.09 ± 0.06	0.27	10	1.02 ± 0.06	0.19
Cardiac output/m²	20	4.37 ± 0.22	0.98	18	4.71 ± 0.22	0.93	13	4.82 ± 0.29	1.06
$\frac{\text{Renal blood flow} \times 100}{\text{Cardiac output}}$	20	13.7 ± 1.08	4.83	18	17.1 ± 0.98	4.26	13	11.9 ± 1.28	4.63

TABLE II

Clinical data in 28 cases of toxae

1st study: shortly after admission. 2nd study: 1–6 weeks after d

Patient No.	Age	FIRST STUDY BSA m²	Time of study	Blood-pressure mm.Hg	Proteinuria per mille	Eye-grounds	Foetus	BSA m²	Time stud W. a.
1	24	1.64	40 w	145/85	4.5	N	living	1.52	1
2	30	1.97	31 w	160/120	6.0	II	living	—	—
		1.97	34 w	150/100	4.5	II	dead	1.95	6
3	32	2.00	37 w	160/105	8.0	I	dead	—	1
4	36	1.76	35 w	150/100	8.0	II	dead	1.69	6
								1.69	16
5	22	1.89	42 w	145/100	0.1	I	living		
6	28	1.48	36 w	170/115	4.0	N	living	1.36	2
7	28	1.73	26 w	190/120	8.0	II	dead	1.63	2
8	31	1.60	35 w	150/110	4.0	I	living	1.52	2
9	18	1.73	40 w	155/115	3.8	II	living	—	—
10	26	1.65	32 w	160/100	3.0	N	dead	—	—
11	28	1.91	38 w	160/110	5.0	I	living	—	—
12	32	2.01	30 w	145/105	0.1	N	living	—	—
		2.02	34 w	160/110	3.3	N	living	1.91	1
13	29	1.85	30 w	180/120	1.4	I	dead	1.78	2
14	32	1.73	29 w	170/115	1.8	N	dead	1.60	2
15	35	1.97	38 w	150/110	1.0	N	living	1.84	3
16	24	1.85	40 w	145/100	0.1	N	living	1.78	1
17	35	1.63	30 w	220/120	8.0	III	dead	1.58	2
								1.58	5
18	28	1.69	38 w	210/150	5.0	III	dead	1.44	4
19	39	1.81	32 w	190/125	7.0	I	dead	—	—
20	35	1.75	37 w	155/100	6.0	I	living	1.66	2
21	31	1.55	28 w	165/95	12.0	I	dead	—	1
22	32	1.84	40 w	180/105	0.2	II	living	—	1
23	23	1.73	36 w	150/100	12.0	II	dead	—	1
24	31	1.85	34 w	165/95	0.1	N	living	—	2
25	22	1.79	44 w	140/105	0.1	N	living	—	2
26	28	1.80	30 w	150/95	0.6	N	living	—	1
27	18	2.03	40 w	170/100	0.1	I	living	—	1
28	26	1.37	37 w	170/120	0.5	II	living	—	1

BLE II

of toxaemia of pregnancy.

eks after delivery. 3rd study: 40–104 weeks after delivery.

SECOND STUDY				THIRD STUDY				
Time of study W. a. d.	Blood-pressure mm.Hg	Proteinuria per mille	Eye-grounds	BSA m^2	Time of study W. a. d.	Blood-pressure mm.Hg	Urine	Eye-grounds
1	130/85	1.0	N	1.52	40	120/80	N	N
—	—	—						
6	140/90	0	N	1.93	14	140/90	N	N
1	—	—	—	1.88	68	120/70	N	N
6	135/85	1.0	—					
16	140/90	1.0	N	1.68	104	130/85	N	N
			—	1.79	40	110/70	N	N
2	135/90	0.4	N	1.33	76	135/80	N	N
2	120/85	0.1	N	1.63	48	135/90	N	N
2	110/80	0.4	N	1.52	52	120/80	N	N
—	—	—	—	1.60	48	145/90	N	N
—	—	—	—	1.53	104	130/80	N	N
—	—	—	—	1.70	64	125/85	N	N
—	—	—						
1	135/90	N	N					
2	140/80	N	N					
2	145/90	N	N					
3	120/85	N	N					
1	130/85	N	N	1.70	48	120/80	N	N
2	140/80	N	—					
5	140/95	N	N	1.58	104	150/110	N	—
4	120/80	N	—	1.44	40	135/95	N	N
—	—	—	—	1.78	40	150/110	N	—
2	125/80	N	N					
1	125/90	N	N					
1	135/85	N	N					
1	120/85	N	I					
2	115/75	N	N					
2	115/75	N	N					
1	130/80	N	N					
1	110/80	N	N					
1	120/85	N	—					

[facing p. 158

TABLE II

Clearance data in 10 cases of toxaemia of pregnan

				FIRST STUDY				
				Clearances ml./min.				
Patient No.	Time of study	Diastolic blood-pressure	Diuresis ml./min.	Inulin	PAH	Creatinine Exog.	Endog.	FF
2	31 w	120	1.5	111	318	130	—	34.8
	*34 w	100	0.9	—	255	74	—	—
7	26 w	120	1.0	80	419	102	—	19.1
10	32 w	100	1.1	—	494	112	—	—
12	30 w	105	3.7	—	748	175	—	—
	*34 w	110	1.5	—	651	133	—	—
13	30 w	120	2.6	136	550	—	103	24.7
14	29 w	115	0.6	20	161	—	23	12.4
17	30 w	120	0.4	—	562	107	—	—
19	32 w	125	1.1	128	383	150	—	33.3
21	28 w	95	0.5	103	773	134	—	13.3
26	30 w	95	2.7	159	572	195	—	27.8

* Excluded

TABLE III(B

Clearance data in 18 cases of toxaemia of pregnan

				FIRST STUDY				
				Clearances ml./min.				
Patient No.	Time of study	Diastolic blood-pressure	Diuresis ml./min.	Inulin	PAH	Creatinine Endog.	Endog.	FF
1	40 w	85	0.7	65	597	88	—	11.0
3	37 w	105	1.6	75	387	97	—	19.1
4	35 w	100	0.4	83	494	—	66	16.8
5	42 w	100	0.6	122	452	134	—	26.8
6	36 w	115	0.8	36	122	43	—	29.8
8	35 w	110	3.9	70	487	131	—	14.4
9	40 w	115	2.1	98	240	—	84	40.8
11	38 w	110	2.9	155	340	166	—	45.5
15	38 w	110	0.8	114	537	114	—	21.2
16	40 w	100	1.7	107	260	—	104	39.5
18	38 w	150	1.6	—	385	102	—	—
20	37 w	100	2.9	85	493	95	—	17.3
22	40 w	105	3.5	91	500	134	—	13.3
23	36 w	100	0.4	—	254	43	—	—
24	34 w	95	0.8	116	681	112	—	17.1
25	44 w	105	4.0	158	367	—	100	42.8
27	40 w	100	1.5	108	—	—	113	—
28	37 w	120	2.3	82	588	125	—	13.9

facing p. 159]

TABLE III(A)

f pregnancy starting before the 33rd week of pregnancy.

	REPEATED STUDY							
				Clearances ml./min.				
FF	Time of study W. a. d.	Diastolic blood-pressure	Diuresis ml./min.	Inulin	PAH	Creatinine Exog.	Creatinine Endog.	FF
34.8								
—	6	90	0.9	120	293	—	96	41
	14	90	0.9	149	386	—	111	38
19.1	2	85	4.3	124	495	137	—	25.1
	48	90	2.0	115	569	—	79	20.1
—	104	80	2.7	139	482	—	116	
—								
—	1	90	4.6	89	551	142	—	16.2
24.7	2	80	0.6	109	288	—	81	37.9
12.4	2	90	6.2	137	461	—	110	22.9
—	2	80	1.2	—	342	126	—	
	5	95	8.1	—	357	130		
	76	110	5.7	128	462	—	110	27.7
33.3	40	110	3.1	130	492	146		26.7
13.3								
27.8								

ABLE III(B)

f pregnancy starting after the 33rd week of pregnancy.

	REPEATED STUDY							
				Clearances ml./min.				
FF	Time of study W. a. d.	Diastolic blood-pressure	Diuresis ml./min.	Inulin	PAH	Creatinine Exog.	Creatinine Endog.	FF
11.0	1	85	16.7	159	688	185	—	23.0
	40	80	2.4	123	510	—	92	24.0
19.1	68	70	8.2	93	446	—	88	20.8
16.8	6	85	3.9	94	358	—	81	29.0
	16	90	2.6	96	325	—	69	27.8
	104	85	1.8	102	354	—	86	24.3
26.8	40	70	1.1	109	364	—	93	30.0
29.8	2	90	4.6	113	402	131	—	28.2
	76	80	3.6	127	531	—	104	24.0
14.4	2	80	7.3	113	396	142	—	28.6
	52	80	3.4	129	509	—	114	29.4
40.8	48	90	6.0	132	700	—	89	18.9
45.5	64	85	7.9	66	348	123	—	17.5
21.2	3	85	2.8	132	432	170	—	30.5
39.5	1	85	—	123	297	—	94	40.9
	48	80	—	122	—	—	108	—
—	4	80	2.8	—	595	181	—	—
	76	95	6.8	139	635	—	105	21.9
17.3	2	80	3.2	122	437	145	—	27.9
13.3								
—								
17.1								
42.8								
—								
13.9								

before the start of the procedure (Alving and Miller, 1940). PAH clearance was determined after one intramuscular injection of PAH given about 1 hour before the start of the urine collection (Bucht, 1949a). The clearance of creatinine was always determined in order to check the emptying of the bladder and possible analytic errors in the inulin analysis. In all cases 3 urine collection periods of 30 minutes each were used. The bladder was washed out twice with 50 ml. sterile water and 50 ml. air after emptying. Blood samples were taken from an indwelling needle in one brachial artery at the start and at the end of each urine collection period.

Methods of analysis, calculations and statistical treatment are described earlier (Bucht, 1951). BSA was computed from Du Bois nomogram, which is generally used even in pregnancy, although it may be a debatable procedure in pregnancy.

In 9 of the cases the cardiac output and total plasma volume were determined simultaneously with the clearance determinations using Evans blue dye, T-1824 (Lagerlöf *et al.*, 1949; Hamilton *et al.*, 1932; Bucht, 1951).

The renal blood-flow was calculated from the PAH clearance, assuming 90 per cent extraction of PAH and using the haematocrit value obtained.

Results

Tables III (A) and (B) contain the results of all clearance determinations. The clearance values are calculated on 1.73 m^2 BSA and are the average of 3 periods.

Fig. 1 shows the distribution of inulin and PAH clearance during toxaemia in comparison with normal pregnancy. The clearance of inulin is lower than normal in toxaemia. In some cases the PAH clearance also is markedly lower than normal, but the spread of the values is greater. Many have PAH clearances within normal limits. The cases are not divided in different groups according to the duration of the pregnancy in this figure.

Fig. 2 shows the statistical treatment of the results. In the statistical analysis the material is divided into 4 groups: "early" which contains the cases with toxaemia starting up to the 9th month of pregnancy and "late" which contains the cases with toxaemia in the 9th and 10th months of pregnancy. The 2 postpartum groups comprise the cases studied 2–7 weeks and 8–48 weeks postpartum.

The inulin clearance is statistically proved to be lower in the early group compared with the normal material (105 ml./min. compared with 170 ml./min.). The inulin clearance in the late group is 98 ml./min. compared with 156 ml./min. in the normal group. This difference is statistically very probable. The PAH clearance is statistically lower in the early and in the late groups than in the normal material (498 in the early and 423 in the late group compared with 800 and 571 in the normals respectively).

The inulin clearance in the postpartum groups is almost identical with the normal material.

The PAH clearance 2–7 weeks postpartum is statistically lower than in the normal group. The difference 8–48 weeks postpartum has, however, no statistical support.

The exogenous and endogenous creatinine clearance usually shows the same changes as the inulin clearance. The quotient exogenous creatinine clearance/inulin clearance (1.32) is higher in toxaemia than in normal pregnancy and even higher than the quotient found in non-pregnant

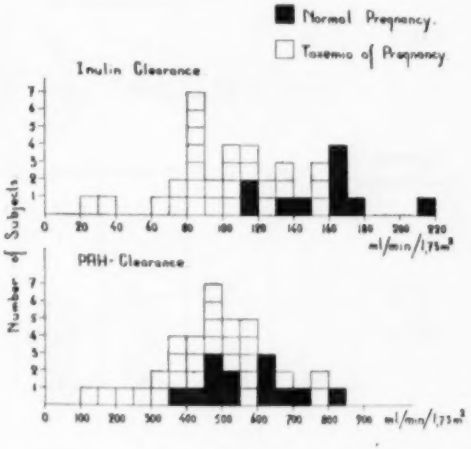


FIG. 1

Distribution of inulin and PAH clearance in normal and toxaemic pregnancy.

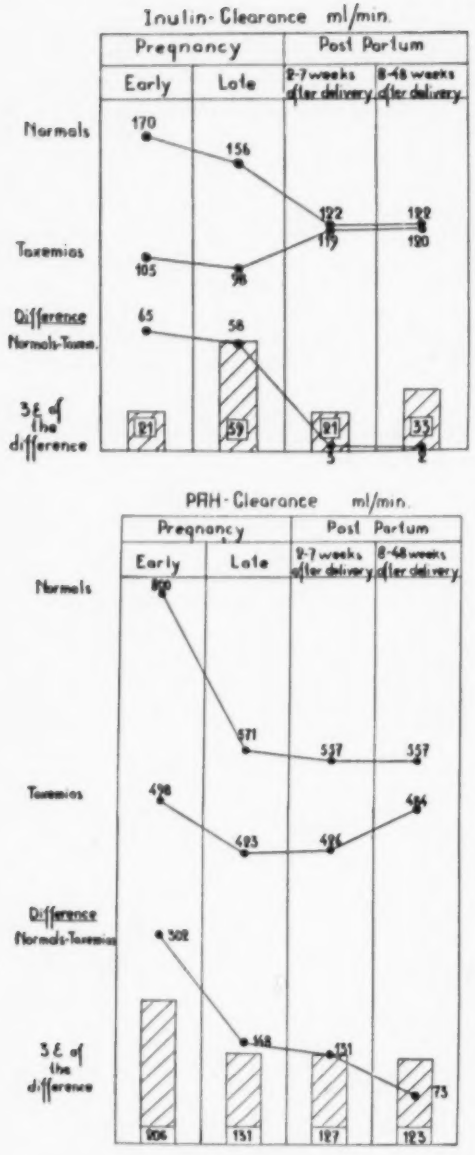


FIG. 2

Inulin and PAH clearance in toxaemia of pregnancy compared with values found in normal pregnancy. Difference exceeding 32 of the diff. is considered statistically significant.

individuals. The results of the creatinine clearance are not given in the figures, as the determinations are too few for statistical analysis.

The mean cardiac output was the same as in normal pregnancy. Hamilton (1950) found increased cardiac output in 17 of 21 cases with toxaemia. This difference may be due to the large spread of values found during pregnancy. The renal fraction of the cardiac output was lower than in normal pregnancy in 7 of the 9 cases studied. The increase in peripheral resistance in toxaemia is thus (in a large percentage of cases) more marked in the kidney than in the rest of the body (Table IV).

The plasma volume is lower in toxaemia than in normal pregnancy. This is in accordance with the findings of White (1950) and others.

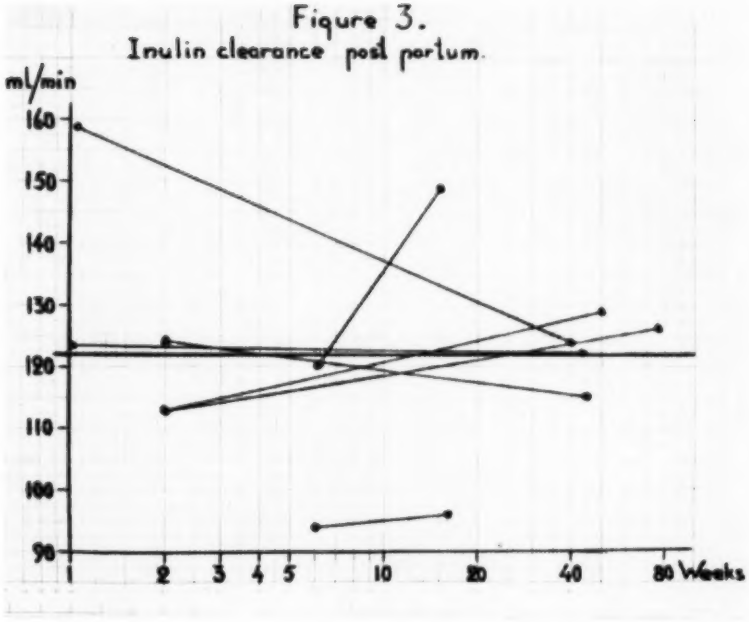
There was no correlation between the amount of proteinuria and the clearance values, nor between eye-ground changes and renal plasma-flow.

Table V shows the correlation between the eye-ground changes, renal clearances and percentage survival of the foetus. The over-all foetal mortality is 46 per cent, which is in accordance with the figure given by Dieckmann (1941). It is of interest that the marked changes in renal function did not increase the foetal mortality rate. The degree of eye-ground changes on the other hand showed a fair correlation with the risk to the foetus. It is also of interest that in 2 cases where repeated determinations of renal plasma-flow were carried out before delivery there was a further decrease of renal plasma-flow although the general condition of the patient improved.

DISCUSSION

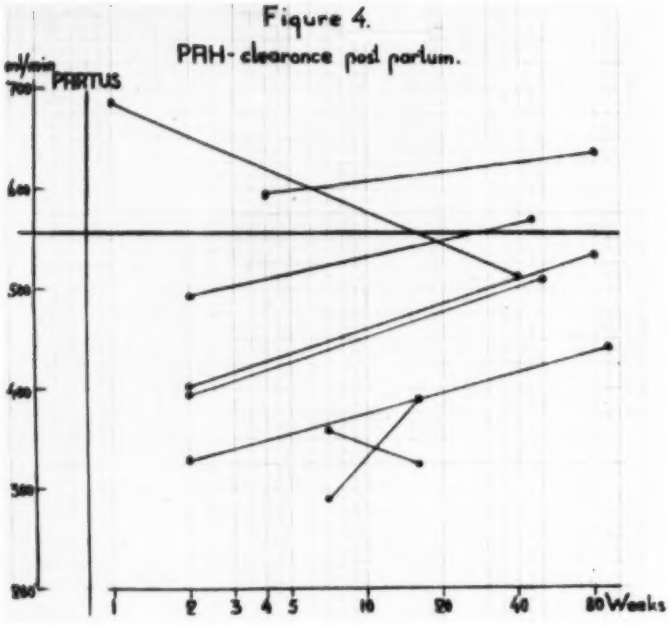
Discussion of the methods

The validity of the results of determination of renal clearance, especially when the blood concentration of the test substance is inconstant, depends to a great extent upon exact emptying of the bladder. During pregnancy this may be difficult. Chesley *et al.* (1940) studied the extent of emptying the bladder and compared the result of the routine procedure with the results obtained after ureteral catheterization with wash-out of the renal pelvis. They did not find any difference and concluded that the routine



Changes in inulin clearance in cases of toxaemia of pregnancy after delivery.

H.B., L.W.



Changes in PAH clearance in cases of toxaemia of pregnancy after delivery.

TABLE IV

Cardiac output, renal blood-flow, and plasma volume in 9 cases of toxaemia of pregnancy.

Subject No.	Total renal blood-flow	CO l/min.		Plasma vol. ml.	Renal fraction per cent
		Total	Per m^2.		
3	783	6.08	3.70	2350	12.9
5	799	9.71	5.88	3110	8.2
6	549	7.09	4.42	3050	7.7
7	751	6.38	3.36	3300	11.7
8	929	5.15	2.98	2700	18.0
10	834	7.66	5.17	2440	10.9
11	670	14.30	7.56	4070	4.7
17	553	8.84	4.42	3330	6.3
19	755	9.00	4.97	2930	8.4

procedure employed gave satisfactory results also in pregnancy. Bucht (1951) compared the delay-time in non-pregnant women and women late in pregnancy and also concluded that the delay-time did not influence the validity of the results obtained in pregnant women. From our data and from those earlier reported the variability in renal clearances seems to be greater in patients with toxaemia than in the normal. This may be due to difficulties in maintaining a high diuresis in these patients.

The concept of inulin clearance as a measure of the glomerular filtration rate has been challenged. Ekehorn (1934) claims that inulin is reabsorbed in the tubules. Results published by Fergusson *et al.* (1950) also speak for the tubular reabsorption of inulin. Some results obtained in our laboratory (Josephson *et al.*, to be published) may also be interpreted as evidence for the tubular absorption of inulin. In spite of this accumulating evidence, the inulin clearance must be considered as the most accurate measure of the glomerular filtration rate in man for the present. Rehberg (1926) used the clearance of exogenous creatinine as a measure of the glomerular filtration rate. Shannon (1935), however, showed that creatinine is excreted through the tubules in man. At the end of normal pregnancy the quotient creatinine clearance/inulin clearance is about 0.98 (Bucht, 1951). Creatinine clearance thus is a fairly good measure of the glomerular filtration rate at the end of normal pregnancy. The clearance of endogenous creatinine during pregnancy is not sufficiently studied and our material is too small to allow any conclusions.

The clearance of sodium thiosulphate was considered to be identical with the inulin clearance and the glomerular filtration rate. The seeming resemblance between inulin and sodium thio-

TABLE V

Foetal mortality in relation to renal function and eye-ground changes in toxaemia of pregnancy.

Foetus	Eye-grounds	Clearance results											
		Inulin				PAH				FF			
		<59	60–98	99–146	>146	<128	129–414	415–700	>700	<17.9	18–27.5	27.6–37.1	>37.1
Living	0	1	1	3	2	1	2	4	1	2	1	2	2
	I	–	2	2	1	–	1	3	–	2	1	–	1
	II	–	3	1	–	–	2	2	–	2	–	1	1
	III	–	–	–	–	–	–	–	–	–	–	–	–
Dead	0	1	–	–	–	–	1	1	–	1	–	–	–
	I	–	1	3	–	–	2	1	1	1	2	1	–
	II	–	2	–	–	–	1	2	–	1	1	–	–
	III	–	–	–	–	–	1	1	–	–	–	–	–

sulphate clearance has been shown to be due to a combined tubular excretion and reabsorption of thiosulphate (Bucht, 1949b). Lambiotte, Blanchard and Graff (1950) demonstrated the similarity between the pregnant and non-pregnant state in this respect.

The validity of PAH and diodrast clearance as measures of the renal plasma-flow in normal or almost normal kidneys is beyond doubt. When the kidneys are damaged by marked toxic or infective agents the ability to excrete nearly all PAH or diodrast at low plasma levels is impaired. Under those circumstances the clearance of these substances does not reflect the plasma-flow but is considerably lower. The only way to get an exact estimation of the renal plasma-flow then is with renal venous catheterization, which permits the determination of the renal extraction of the test substance. There is no reason to believe that toxaemia of pregnancy would depress the tubular function to such an extent that the extraction of PAH or diodrast would be altered. Renal venous catheterization was not performed to control this extraction late in pregnancy due to technical difficulties. One case was catheterized 4 months postpartum. The renal extraction of PAH was normal although the renal plasma-flow was somewhat depressed. It cannot be excluded that the cases with extremely low PAH clearance have a decreased PAH extraction. The equally depressed inulin clearance in those cases indicates a low plasma-flow. In the following the PAH-clearance will be considered as a true measure of the renal plasma-flow also during toxaemia of pregnancy, although it is admitted that absolute proof is lacking. Work in progress in this laboratory aims at the solution of this question.

Discussion of the results

The present study confirms the general finding that the inulin clearance in toxaemia is low and shows that this decrease is much more marked than was generally thought. In normal pregnancy the inulin clearance is increased (Bucht, 1951). Those cases especially which develop toxaemia early in pregnancy have a reduction of glomerular filtration rate about 50 per cent of what is normal for the month of pregnancy.

The cause of low inulin clearance is not known, but many theories have been brought forward. Chesley *et al.* (1940) and Corcoran and Page (1941) are of the opinion that increased pressure in the glomerular capsule with oedema in the basal membrane of the glomerulus caused decreased filtration. That swelling of the basal membrane is a possible cause was first pointed out by Bell (1932). Kellar (1939) likewise found increased thickness of the basal membrane in cases of toxaemia that were studied postmortem. The presence of oedema in the membrane has, however, not always been demonstrated.

Kenney *et al.* (1950) calculated the segmental resistance in the renal vascular bed and found increased resistance mostly in the afferent vessels. This should give a decreased filtration pressure, diminishing the filtration rate. In our material there was a rapid restitution of the inulin clearance to normal within 2 weeks after delivery (from 100 to 122 ml./min.) without any further changes up to 2 years afterwards. The rapid increase in filtration rate may be interpreted in favour of both arteriolar spasm and glomerular oedema as causes of decreased filtration before delivery. Organic changes in the glomerular membrane could not alter so rapidly.

To differentiate between oedema or spasm is not possible without knowledge of the renal tissue pressure. The calculations of Kenney are based on the fundamental assumption that there is no change in renal venous or tissue pressure and that the only alteration in the kidney during toxaemia is circulatory. It is obviously impossible to apply any formula for calculation of segmental resistances in the kidney during the marked changes in kidney function in toxaemia of pregnancy. A moderate oedema within the renal capsule would give a marked resistance to the circulation without any vascular spasm.

That the quotient creatinine clearance/inulin clearance in toxaemia is higher than in normal pregnancy may be due to increased pressure in the glomerular capsule. As inulin is a much larger molecule than creatinine increased resistance to filtration would influence inulin more. This speaks in favour of the oedema theory. The altered quotient may, however, also be due to changes in tubular function.

PAH clearance is lower in our cases of toxaemia of pregnancy than in normal pregnancy

or in the non-pregnant woman. This is most marked in the cases developing toxaemia early. There was no change in PAH clearance immediately (2–6 weeks) after delivery, but in most cases the renal plasma-flow slowly increased towards normal during the following years. The studies performed 1–2 years after the toxaemic pregnancy still resulted in values for renal plasma-flow lower than normal, although the blood-pressure was normal and none of the patients exhibited any signs of renal disease. The finding of decreased renal plasma-flow during toxaemia of pregnancy is in accordance with the results of Kenney, while Chesley *et al.*, Corcoran and Page, Wellen *et al.*, and Dill *et al.* all state that there is essentially normal renal plasma-flow in toxaemia. Wellen *et al.*, however, found in a few cases repeatedly studied, as we do, that the diodrast clearance showed a progressive decline during toxaemia. All these investigators related their values to non-pregnant control in the erroneous belief that normal pregnancy does not influence renal plasma-flow. Furthermore, the cases studied have been few and, as the spread is large, this may give rise to widely divergent opinions. In our material the extreme values for PAH clearances are 161–866 ml./min. The large spread is due to the differing severity of the disease and also to a differing degree of renal involvement. The cases with higher diastolic blood-pressure generally had lower plasma-flow than those with lower blood-pressure (Table II). This was true regardless of the date in pregnancy when the toxaemia started. This correlates the blood-pressure and the renal circulation, but the mode of connexion may be different. Decreased renal blood-flow may give increase of blood-pressure. Dexter and Haynes (1944) have demonstrated increased content of renin in the blood in eclampsia. On the other hand general arteriolar contraction will give both increased blood-pressure and decreased renal blood-flow.

The renal plasma-flow does not increase until several months after delivery. The regulation of the circulation at the end of pregnancy and in the immediate postpartum period is poorly understood and it is impossible to draw any conclusions from our data regarding the regulation of the renal circulation during this period.

It is of interest, however, that there is a gradual increase toward normal values for a considerable period after the toxaemic pregnancy. The prognostic importance of this is not clear, but it should be pointed out that all cases except 2 had normal blood-pressure at follow-up, a finding at variance with those of Chesley.

The filtration fraction has been found to be high or low in toxaemia of pregnancy. Corcoran and Page (1941) classified their cases according to the filtration fraction and found a better prognosis in cases with high FF than in those with low FF. The use of FF to judge the extent of renal changes or the nature of the changes is impossible. We also feel that it is impossible to use the figure for FF to decide whether a case has had hypertension before or not. In our material the values for FF showed a large spread without any correlation with the clinical state of the patient. It is noteworthy that some cases at follow-up had a high filtration fraction but normal blood-pressure.

A normal cardiac output occurring with increased blood-pressure denotes increased peripheral resistance. The decreased renal fraction of the cardiac output, found in 7 out of 9 cases, demonstrates that the resistance in the renal vascular bed was more marked than elsewhere in the periphery.

Although much work has been done to find the agent responsible for the increased peripheral resistance in toxaemia of pregnancy no one has succeeded in finding any specific substances. Nor-adrenalin, given intravenously, causes an increased peripheral resistance and decreased renal blood-flow without any change in cardiac output and decreased sodium excretion, that is the changes found in toxaemia. We have assayed the excretion of nor-adrenalin in Cases 2 and 4. In Case 2 the excretion of nor-adrenalin was increased, in Case 4 it was normal. It is thus possible that nor-adrenalin in some cases may cause some of the changes found in toxaemia.

Summary and Conclusions

(1) The renal clearance of inulin and para-amino-hippuric acid was studied in 28 cases of toxaemia of pregnancy. In all cases the study was repeated once or twice after delivery up to 2 years after delivery.

(2) The validity of the methods is discussed. It is concluded that inulin clearance is the best measure of glomerular filtration rate and PAH-clearance of the renal plasma-flow in toxaemia of pregnancy.

(3) Inulin clearance is lower than normal in toxaemia of pregnancy, but it undergoes a rapid increase after delivery. This speaks against organic changes as a cause of decreased filtration rate. Other possible causes are discussed.

(4) The PAH clearance is also lower than normal in toxaemia of pregnancy. The PAH clearance does not increase to normal immediately after delivery but increases slowly, and in some cases not at all. These latter cases do not necessarily develop arterial hypertension within the time of observation (2 years).

(5) The filtration fraction did not show any typical changes in toxaemia of pregnancy.

(6) There was no correlation between the extent of renal changes and the death of the foetus.

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A STUDY OF THE RENAL TRACT IN CARCINOMA OF THE CERVIX

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DURING the past few years an attempt has been made to carry out a careful investigation of the urinary tract in patients suffering from carcinoma of the cervix.

Review of the Previous Literature

Ewing (1922) and Warren (1931) have stated that most cases of carcinoma of the cervix die from uraemia due to ureteral obstruction. From postmortem studies, Wagner (1858) found that one-third of his cases showed ureteral involvement, and 37 years later Williams (1895) reported an incidence of hydronephrosis and hydroureter in 85.9 per cent of cases. In a similar series Faerber (1931) reported ureteral obstruction in 56 per cent and Behney (1933) 65 per cent. More recently Graves, Kickham and Nathanson (1936) found hydronephrosis in 79.3 per cent of 87 cases studied by them at autopsy. Ten of these cases received no treatment. In 1947, De Alvarez in an analysis of the causes of death in carcinoma of the cervix found that 40 per cent of the patients died from invasion of, or obstruction to, the genito-urinary tract.

In 1926 clinical demonstration of ureteral obstruction was reported by Herger and Schreiner, who found dilatation in the ureters and renal pelves in 48 per cent of cases out of a total of 50 examined, and Colby (1933) using the intravenous pyelogram found an incidence of abnormality in 35.1 per cent of cases. Drexler and Howes (1934) report 68 per cent of abnormalities on cystoscopic examination of cases showing extension of the tumour into the broad ligament.

Graves, Kickham and Nathanson (1936) reported extensively on 257 cases studied at the Pondville Hospital, Massachusetts. Obstruction demonstrated by ureteral catheterization occurred in 37.3 per cent of 67 cases and retrograde pyelography on 32 cases showed obstruction in 81.3 per cent. Intravenous pyelograms were carried out on 40 cases and demonstrated dilatation or absence of excretion in 77.5 per cent.

A further paper was published from the same centre in 1940 by Jaffe, Meigs, Graves and Kickham and, out of 70 cases who had been followed 5 years or more, 25 were found to have ureteral obstruction. Of these 25 patients 13 had shown evidence of obstruction before treatment. In 1947 Pomeroy reported an incidence of abnormality of 16.2 per cent of 271 cases, whilst Long and Montgomery (1950) reported on 116 cases, and Aldridge and Mason (1950) 333 cases, showing an incidence of abnormality in 53.4 per cent and 34 per cent respectively.

Newcastle Series

The present study was carried out on 428 patients treated by the Newcastle Regional Cancer Organization between 1947 and 1951. Three hundred and twenty-seven of these patients were studied before the commencement of treatment. During this time a total of 750 patients have been treated, but only since February 1949 have facilities existed for performing excretion urography on every patient admitted. More recently in the investigation renal function tests have been performed to compare with the pyelograms, but it is considered that further work is essential before comment can be made on these results. The treatment of the majority of these patients has been by radium or a combination of radium and surgery, according to the response of the tumour to irradiation (Glucksmann and Way, 1948). X-ray therapy has not been used.

Incidence of Abnormalities Before Treatment

There are 327 pre-treatment pyelograms available for analysis. Abnormality was based upon the finding of hydronephrosis, hydroureter, non-excretion of the kidney, or poor concentration of the dye. Table I (A) shows an incidence of abnormality in 29.6 per cent of cases.

TABLE I (A)

Incidence of Abnormality in Pre-operative Pyelograms
Percentage figures shown in parenthesis

	Total	Abnormal	Bilateral	Unilateral
Pyelograms	327	97 (29.6)		
Stage I	70 (24.7)	8 (11.2)	4 (50.0)	4 (50.0)
Stage II	180 (80.4)	44 (24.5)	9 (30.5)	35 (79.5)
Stage III	41 (14.4)	21 (51.2)	6 (28.0)	15 (72.0)
Stage IV	36 (12.9)	24 (66.6)	10 (41.6)	14 (58.4)

It might be assumed that the vast majority of abnormal pyelograms would be detected only in cases with very advanced tumours, but Table I (A) shows that, although the incidence increases steadily from Stage I to IV, and although there is a very marked increase in abnormalities in Stages III and IV as compared with Stages I and II, there is nevertheless an incidence of 24.5 per cent in Stage II. Since this type of case constitutes more than half of those referred to this centre, this figure of nearly 25 per cent is one of great importance, as will be shown later. Excluding Stage I where the total number of abnormalities is very small it will be seen that the incidence of bilateral abnormalities increases in accordance with the stage of the disease.

Table I (B) shows a comparison of the findings in this series with those published by Aldridge and Mason. The close similarity of the findings in both series will be seen. Most other authors do not refer to the stage of the disease in their writings or they do not use League of Nations staging, but the figures of Pomeroy (1947) are quoted because it is a large recent series (see Table I (C)).

The staging used by Pomeroy is not that of the League of Nations but one peculiar to his own clinic. From his paper it is not possible to translate these figures into League of Nations staging but it would appear that his Stages I, II, and III correspond to League of Nations I and II, whilst his Stage IV probably represents both Stages III and IV League of Nations.

TABLE I (B)

Comparable Abnormality in Stages (Per cent)

		Aldridge and Mason
Stage I	11.2	14.5
Stage II	24.5	22.0
Stage III	51.2	59.0
Stage IV	66.6	
Total	29.6	34.0

Other authors' staging transformed into comparable League of Nations staging from definition stated.

TABLE I (C)

Incidence of Abnormal Pyelograms
(Pomeroy)

	Normal	Abnormal	Percentage
Stage I	17	0	0
Stage II	56	1	1.8
Stage III	137	20	14.6
Stage IV	40	17	42.5

The findings in this series have been based on excretion urography but Graves *et al.* (1936) suggest that an even higher percentage of abnormalities of the urinary tract would be revealed if retrograde pyelography was carried out in those cases which showed a normal intravenous pyelogram. From the present study it is impossible to confirm or refute this statement as facilities for carrying out retrograde pyelography in this large number of patients have not been available so far, but in view of their findings a further study on these lines is indicated.

Prognosis

It has been stated repeatedly in the American radiotherapeutic literature that any case of carcinoma of the cervix showing an abnormal

pre-treatment pyelogram should be relegated to Stage IV irrespective of other findings. This has never been practised in this clinic since it is an axiom of the League of Nations sub-committee that all staging should be based on clinical findings only. Nevertheless, these repeated vague statements in the literature would seem to suggest that a very low survival rate had been found in cases with an abnormal pyelogram and which had been treated radiotherapeutically, even though no very clear evidence for this can be found.

In this study 264 patients were investigated more than 1 year ago and an analysis of the results of treatment at 1 year are shown in Table II.

TABLE II

Survival at One Year

Percentage figures shown in parenthesis

Total number of pyelograms	264
Normal pyelograms	189
Abnormal pyelograms	75 (28.4)
Deaths in first year—normal pyelogam	60 (31.7)
Deaths in first year—abnormal pyelogram	53 (70.6)

Stage	Total number of cases	Abnormal pyelogram		Normal pyelogram	
		Dead at one year	Alive at one year	Dead at one year	Alive at one year
I	70	4 (50.0)	4	14 (22.5)	48
II	149	26 (66.6)	13	34 (30.8)	76
III	33	17 (81.0)	4	8 (66.6)	4
IV	12	6 (85.7)	1	4 (80.0)	1

There were 189 patients showing a normal pyelogram. Sixty (31.7 per cent) died within the first year of treatment. Of 75 patients with abnormal pyelograms before treatment 53 (70.6 per cent) died in the first year. Thus the mortality rate in the first year after treatment is more than twice as great in the group showing abnormalities as in those whose urinary tract is normal. It will be seen from the detailed analysis in Table II that the mortality in cases with an abnormal pyelogram in Stages I and II is also twice that of those showing no abnormality, and for this reason an abnormality in the pre-treatment pyelogram must be regarded as a finding of grave prognostic significance.

The mortality during the first year in Stages III and IV with a normal pyelogram is so great in itself that a figure of double this for the abnormal group could not be obtained. Even so, the death rate in Stage III cases showing abnormalities of the pyelogram is considerably higher than those with a normal pyelogram.

Everett (1947) reported 46 cases, 16 of which had an abnormal pre-treatment pyelogram, all of whom failed to survive, and Aldridge and Mason report a gross 5-year survival in only 16 per cent of their normal cases. All authors stress the seriousness of abnormalities as a pre-treatment finding, and attempts to treat these abnormalities by operations on the urinary tract, such as ureteric dilatation, nephrostomy, etc., meet with little success. This would indicate that these abnormalities are due to extensions of the tumour which are not always apparent clinically. Evidence to show that this is so will be given later.

It will be seen from Table II that, of 39 cases with an abnormal pyelogram in Stage II, 66.6 per cent died in the first year and when it is appreciated that more than half of the total cases seen in this clinic fall into this group the importance of finding urological abnormalities here becomes apparent not only in evaluating prognosis but also in considering the line of treatment.

Clinical Examination correlated with Urography

The routine clinical examination of patients in this series consisted of cystoscopy, a com-

bined rectal and vaginal examination and inspection of the cervix under anaesthesia. The staging was based on this examination with the exception of a very few cases which were placed in Stage IV as a result of extra-pelvic metastases found on general clinical examination of the patient.

Clinical Examination of the Broad Ligaments

The reason usually advanced for the cause of ureteral obstruction in cases of carcinoma of the cervix is that of extension of the tumour into the broad ligament. This view was the result mainly of autopsy findings, but in the light of studies on operative specimens many of the thickenings felt on clinical examination were proved to be not neoplastic.

Table III (A) shows the results of clinical examination of the broad ligaments correlated with pre-treatment pyelogram findings. These clinical findings are of some interest as in a number of cases subsequent histological examination of the broad ligament was possible.

TABLE III (A)

Clinical Examination of the Broad Ligaments
Percentage figures shown in parenthesis

	No thickening in broad ligaments	Thickening in broad ligaments
Normal pyelogram	136 (86.2)	136 (66.7)
Abnormal pyelogram	22 (13.8)	68 (33.3)
Total	158	204

Out of a total of 158 cases with no palpable thickening in the parametria, 22, or 13.8 per cent, showed an abnormal pyelogram. In 204 cases in which thickening was felt in the broad ligament the incidence of abnormality of the pyelograms was 33.3 per cent, and in the more detailed analysis of the clinical findings in the broad ligament shown in Table III (B) it will be seen that there is close correlation in 62 out of 98 cases, but that in 36 there appears to be no correlation between the clinical findings and those which might be expected on radiological examination. The evidence produced by these tables would suggest that neoplastic involvement of the broad ligaments is responsible for a number of urinary tract abnormalities but the 13.8 per cent incidence of abnormality in cases with no thickening in the broad ligament and the 36 cases in Table III (B), in which the clinical and radiological findings did not correspond, would suggest either that clinical examination is unreliable or that some other cause of obstruction is present. Evidence to show that both these statements are correct is produced in a later section of this paper.

TABLE III (B)

Analysis of Clinical Findings in Broad Ligaments compared with Pyelogram Findings
(Abnormal pyelograms only)

Unilateral abnormal pyelogram with involved ligament on the same side	16
Unilateral abnormal pyelogram with bilateral involvement of ligaments	31
Bilateral abnormal pyelogram with one ligament involved	8
Bilateral abnormal pyelogram with bilateral involvement	15
Unilateral abnormal pyelogram with non-involved ligaments	17
Bilateral abnormal pyelogram with non-involved ligaments	6
Unilateral abnormal pyelogram with involvement of opposite ligament	5

Cystoscopic Findings

Since the majority of the cases in Stage IV were so staged because of obvious involvement of the bladder base they are excluded from this discussion which is based on deviations from the normal other than obvious involvement of the bladder with tumour. Out of 344 cystoscopies, 273 were normal and 71 (20.3 per cent) were abnormal. These cases have been followed up from 6 months to 5 years and it will be seen from Table IV (A) that slightly more than half of the cases with the abnormalities enumerated in the table are dead.

It will be seen from Table IV (B) that an abnormal pyelogram, whether it be associated with normal or abnormal bladder findings, gives a very high mortality in the first year. Abnormal cystoscopic findings in conjunction with a normal pyelogram show a mortality of 51 per cent in the first year.

TABLE IV (A)

Detailed Analysis of Cystoscopic Findings

Abnormality	Alive	Dead	Total
Injection	8	2	10
Dilated veins	6	4	10
Cystitis	8	8	16
Displacement of bladder wall	1	3	4
Oedema other than bullous	11	15	26
"Granuloma"	0	3	3
Petechial haemorrhage	1	0	1
? Tumour	0	1	1
	35	36	71

Total number of normal cystoscopies 273
Incidence of abnormality, per cent 26

dosage than any tumour that may have been in the broad ligaments.

Table V shows the cases in which histological examination of the broad ligaments was possible, correlated with the urographic findings. It will be seen that the incidence of the abnormal pyelogram is twice as high in the group in which the ligaments were found to contain tumour.

Doubts have been cast already in this paper on the reliability of clinical examination as a method of assessing the presence of tumour in the broad ligament. In Stage II cases clinical assessment of the state of the broad ligaments has been found to be unreliable as a result of a study of 57 cases in this clinic. Clinical involvement was found to be present in one or other ligament on 51 occasions but histologically only 12 of these contained tumour tissue, so that the error in clinical assessment was 76 per cent. Sixty-three other cases in Stage II, in which clinical examination failed to reveal involvement, may be compared with these. Fifty-nine of this last group showed no tumour on histological examination. The error here is only 6.3 per cent.

In 30 cases in Stage I, in which all 60 broad ligaments were regarded as not involved, 2 were found to contain tumour on section, an error of

TABLE IV (B)

Survival of Treated Cases, excluding Stage IV and Operative Deaths, showing Urinary Tract Abnormalities

Percentage figures shown in parenthesis

	Total	Died in first year
Abnormality of pyelogram but cystoscopic findings normal	49	39 (80.0)
Normal pyelogram but cystoscopic findings abnormal	71	36 (51.0)
Abnormal pyelogram and cystoscopic findings abnormal (Two of the survivors are less than 6 months)	26	22 (84.6)

Pathological Findings correlated with Urography

Having discussed the intravenous pyelogram in its relation to clinical findings it is now possible to turn to the pathological material made available by operation and autopsy.

Histological Examination of the Broad Ligaments

Before discussing the histological findings in the broad ligaments it should be pointed out that a large number of these cases have been irradiated before operation. It may therefore be argued that some of these broad ligaments may have contained tumour before irradiation. However, since the patients were operated upon because the primary tumour showed resistance to radium and since residual tumour was found in the cervix in every case, it seems reasonable to assume that in no case did tumour disappear from the parametria as a result of irradiation, particularly in view of the fact that the tumour in the cervix was much closer to the source of the irradiation and, therefore, received a larger

TABLE V

Cases with Histological Examination of the Broad Ligaments

Percentage figures shown in parenthesis

	Total	Ligaments not involved	Ligaments involved
Normal pyelogram	95	74 (87.8)	21 (22.2)
Abnormal pyelogram	20	11 (55.0)	9 (45.0)

6.6 per cent. Thus when all these cases with negative broad ligaments, as judged by clinical examination, are interpreted as not containing tumour, the error is only 6.4 per cent as proved by histological examination but, when thickenings in the broad ligament are interpreted as meaning the presence of growth, the error is as high as 76 per cent.

It would appear from this that thickenings may be present in the broad ligament due to factors other than tumour. Some speculation exists as to the nature of these thickenings but at present insufficient material is available in this series to allow any conclusions to be drawn in this respect, but many suggestions have been put forward by others, for example thickenings due to infection or stromal reaction produced by the tumour (Way, 1951).

Lymph Node Involvement

In looking for further causes of ureteral obstruction the possibility of lymph node involvement became apparent from observations made at autopsy. In Table VI (A) an analysis of node involvement in cases studied by pyelogram is set out. In considering these results it has been necessary to consider the pyelogram not only as a whole but also as consisting of two parts, namely left and right, as in some cases unilateral abnormality exists with involved nodes on the same side whilst the opposite side is normal and shows no node involvement. Table VI (B) sets out a more detailed analysis of node involvement correlated with pyelogram findings.

An attempt has been made to correlate histology of the broad ligaments and nodes in the same cases against pyelographic findings, but the number of cases in which abnormalities are found is too small to warrant any conclusions being drawn.

These figures were taken, except for a few autopsies, from cases submitted to laparotomy with a view to Wertheim's hysterectomy, and many had to be abandoned owing to fixity of bladder or nodes. It may be pointed out here that abnormality of pyelogram due to node involvement may be higher than the figures show, as these findings are based on *histological* evidence only and several cases which were inoperable due to fixed nodes were excluded because no nodes could be removed for histological examination. From Table VII it will be seen that there were 72 cases with non-involved ligaments and normal pyelograms. Node involvement was found in 36.1 per cent of cases in this group. These nodes were not particularly enlarged and could not have obstructed the ureter in the state at which they were found at operation. There is little evidence from the operative findings to suggest that node involvement alone causes ureteric obstruction but conclusive evidence for this has been found in a number of autopsies.

TABLE VI (A)
Node Involvement in Cases Studied by Pyelogram
Percentage figures shown in parenthesis

	Total	Nodes not involved	Nodes involved on same side	Unilateral involvement	Bilateral involvement
Normal pyelogram	134	79 (59.0)	55 (41.0)	20	35
Unilateral abnormal pyelogram	22	5 (22.7)	17 (87.3)	12	5
Bilateral abnormal pyelogram	5	2	3		
Total abnormal pyelograms	27	7 (26.0)	20 (74.0)		

TABLE VI (B)

Unilateral nodes involved with normal pyelogram	20
Bilateral nodes with normal pyelogram	35
Bilateral nodes with bilateral abnormal pyelogram	2
Bilateral nodes with unilateral abnormal pyelogram	5
Unilateral nodes with corresponding abnormal pyelogram	9
Unilateral nodes with contra-lateral abnormal pyelogram	3
Nodes negative with unilateral abnormal pyelogram	5
Nodes negative with bilateral abnormal pyelogram	2
Nodes negative with normal pyelogram	76
Unilateral nodes with bilateral abnormal pyelogram	1

TABLE VII
Analysis of Pyelograms in Cases with Histological Examination of Broad Ligaments and Nodes
Percentage figures shown in parenthesis

Negative broad ligaments and normal pyelograms	
Total	72
Nodes involved	26 (36.1)
Positive broad ligaments and normal pyelograms	
Total	21
Nodes involved	12 (57.1)
Negative broad ligaments and abnormal pyelograms	
Total	8
Nodes involved	1
Positive broad ligaments and abnormal pyelograms	
Total	9
Nodes involved	9

Autopsy findings

In this series 71 autopsies were performed. Some of these were incomplete as they were done in difficult circumstances, often in the patient's home, but in 59 cases sufficient evidence is available to demonstrate ureteral obstruction in 44 (74.6 per cent). In all but 4 of these cases (and these will be discussed later) obstruction was brought about by tumour. In Table VIII the causes of ureteric obstruction are set out.

TABLE VIII
Evidence of Obstruction to the Ureters from Autopsies

Obstruction due to tumour in broad ligament	13
Obstruction by involved lymph nodes	10
Obstruction by lymph nodes on one side and tumour in broad ligament on the opposite side	2
Local extension other than broad ligament ...	2
Remote metastases (including 1 due to lymph nodes also)	2
Gross pelvic involvement (? nodes ? broad ligament)	6
Permeation of periureteral lymphatics	4
Post-operative infection	1
Radium necrosis	4
Total	44

There were 15 cases with extensions of the tumour into the broad ligament and 12 cases in which lymph node involvement alone obstructed the ureter. In two of these cases there were masses of involved para-aortic nodes obstructing the ureter (Fig. 1) causing hydronephrosis above, but below the obstruction a collapsed ureter was seen in a pelvis which was free from tumour. In a further case there was a large mass of lymph nodes at the brim of the pelvis in a case which had had a Wertheim's operation 3 years before. In this case also there was no local recurrence.

In the 2 cases with remote metastases follow-up pyelograms showed a gradual downward displacement of an otherwise normal kidney long before any clinical evidence of metastases was present. At autopsy this displacement was found to be due in 1 case to a secondary deposit in the supra-renal which was 4 inches long and 2½ inches wide, and in the other it was due to an enormous secondary in the liver. The total weight of the remaining liver and the tumour was 11 pounds. Fig. 4 shows the radiograph of the urinary tract in this patient shortly before death.

There were 6 cases in which the pelvis was solid with tumour and it was quite impossible to determine whether this extension was from the primary or from lymph nodes.

There were 4 cases showing periureteric lymphatic invasion, one of which had invasion as far up as the renal pelvis. A section of the ureter in one of these cases is shown in Fig. 2. Periureteric lymphatic invasion was described by Carson (1925) and in 1947 DeAlvarez stated that death occurred " as a result of periureteric lymphatic invasion by cells in the retroperitoneal nodes or by invasive spread in the urinary tract itself."

Radium necrosis was seen to have resulted in ureteral obstruction in at least 4 cases. In each case increasing hydronephrosis was observed before death in repeated pyelograms. If these patients had not been submitted to autopsy their deaths may well have been attributed to recurrent tumour. Fig. 3 shows a section of the necrotic ulcer in one of these cases.

Radiation Histology

Table IX shows the incidence of abnormal and normal pyelograms according to (*a*) the response of the tumour to irradiation as judged by the cell count technique and (*b*) the tumour type. There are significantly more abnormalities of the urinary tract in cases which show resistance to irradiation and it is a common finding that these tumours tend to be more widespread

and to metastasize more freely than those which are radio-curable. The difference between the incidence in abnormal pyelograms in cases classified on a broad histological basis of differentiating and anaplastic tumours is not so marked and the two parts of Table IX give further evidence in support of the contention of Glucksmann that individual tumour response is more important than tumour type in relation to ultimate prognosis.

TABLE IX

Incidence of Normal and Abnormal Pyelograms according to the Response of the Tumour to Irradiation

Percentage figures shown in parenthesis

Response	Total No.	Normal	Abnormal
Favourable	43	41 (95.4)	2 (4.6)
Unfavourable	204	144 (70.6)	60 (29.4)

Incidence of Normal and Abnormal Pyelograms according to Tumour Type

	Total No.	Normal	Abnormal
Differentiating tumour	37	27 (73.0)	*10 (27.0)
Anaplastic tumour	154	102 (66.1)	52 (33.9)

*All these cases showed an unfavourable response.

The Use of Pyelography in the Follow-up of Treated Cases.

During the course of this study and as a result of it the value of intravenous pyelography in the after-care of the treated patient became apparent and Table X shows the findings in 69 patients on whom a repeat pyelogram was carried out 1 year after treatment. In all these cases the pre-treatment pyelogram was normal. It is apparent from this table that the development of an abnormality of the pyelogram after treatment is a finding of the utmost gravity.

TABLE X

Follow-up Pyelograms of Cases with Normal Pre-operative Pyelogram and Subsequent Survival

Percentage figures shown in parenthesis

Total number of cases	69
Total deaths from cancer	20 (28.9)
Total deaths from necrosis	4 (5.8)
Normal pyelogram at 1 year	40 (57.9)
Patients alive and well	37 (92.5)
Patients dead	3 (7.5)
Abnormal pyelogram at 1 year	29 (42.1)
Patients alive and well	8 (27.6)
Patients dead	21 (72.4)
from cancer	17 (58.4)
from necrosis	4 (13.7)

In a total of 59 abnormal pyelograms after treatment and irrespective of the findings in the pre-treatment radiograph, pelvic or abdominal recurrence was found in every case. In 19 (32.2 per cent) there was radiological evidence of a urinary tract abnormality before there was clinical evidence of recurrence. The longest interval between pyelographic evidence and clinical signs was 9 months. Fig. 5 shows the first radiographic evidence of an abnormality—a right hydronephrosis. Fig. 6 shows a radiograph taken in the terminal stages of the disease and after clinical evidence of recurrence had been noted. There is now no secretion by the right kidney and a gross left hydronephrosis.

At autopsy on this patient a large right hydronephrosis was found with gross atrophy of the renal cortex. The right ureter was strangled in a mass of recurrent tumour at the site of the previous node dissection. The nodes removed from this area 4 years before had contained cancer. The left kidney showed a moderate hydronephrosis and there was little destruction of the kidney substance. The left ureter was moderately dilated and obstructed in a mass of growth on the left lateral wall of the bladder. In this case the first abnormality noted after treatment was a right hydronephrosis at 27 months. At 36 months after treatment there was clinical evidence of recurrence in the right side of the pelvis and at 42 months the right kidney did not secrete and the left was hydronephrotic.

Although there can be no doubt that a hydronephrosis developing after treatment is of the gravest prognostic significance not every hydronephrosis is due to recurrent tumour as can be seen from Table X. In this series there were 4 cases which were due to radium necrosis. Unfortunately the full significance of this was not fully realized in these 4 cases and, when it was, renal damage was so great that attempts to overcome the obstruction by surgical means led to the deaths of all 4 patients. Fig. 7 shows the radiograph of one of these cases who developed

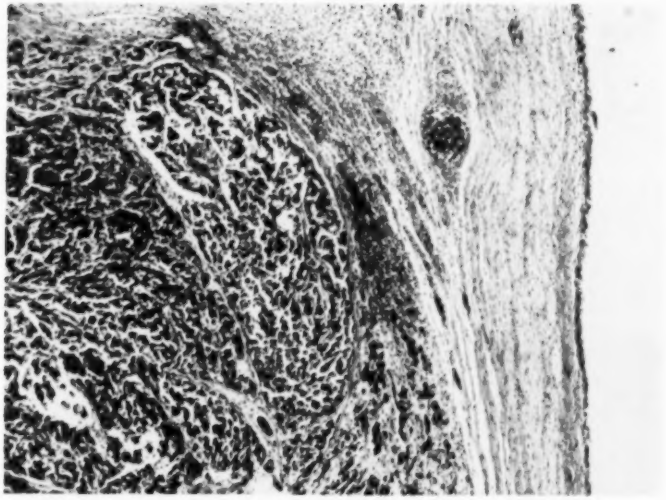

FIG. 1
Section of mass of involved lymph nodes obstructing ureter.
× 50

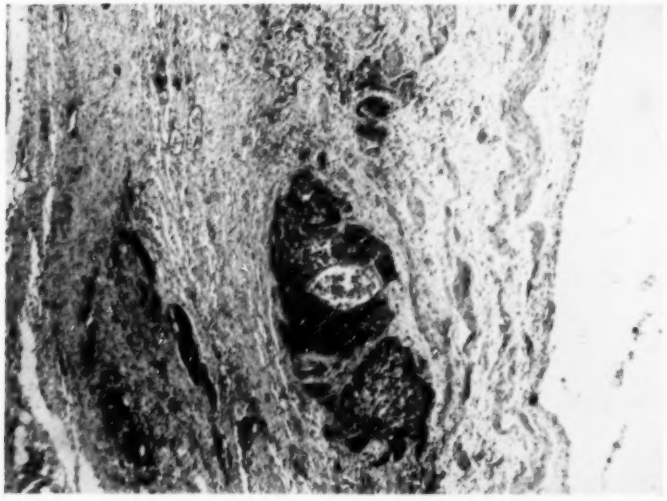

FIG. 2
Section of ureter showing periureteric lymphatic invasion with tumour.
× 56

R.D.

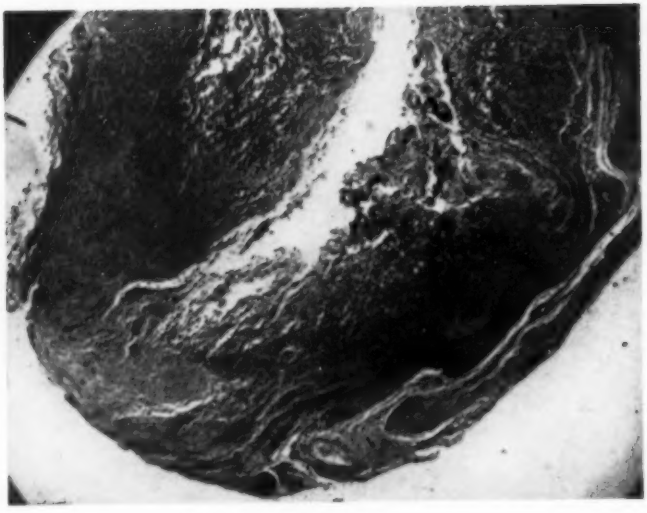

FIG. 3
Section of ureter showing radium necrosis. × 20

FIG. 4

Radiograph showing displacement of right kidney.

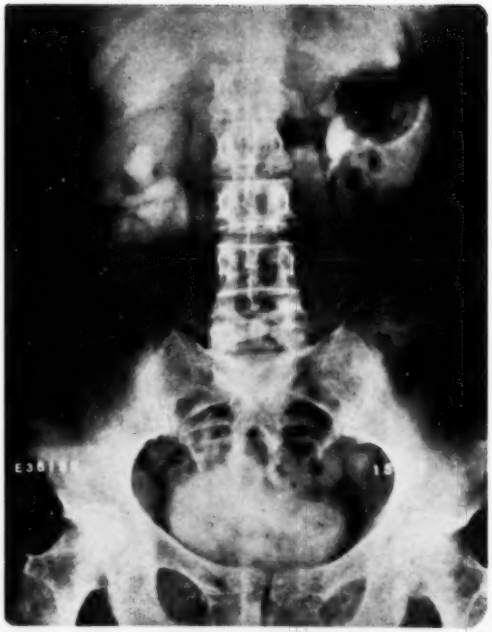

FIG. 5

Radiograph showing right hydronephrosis before recurrence was apparent clinically.

FIG. 6

Radiograph showing no excretion by the right kidney and a left hydronephrosis taken after recurrence became apparent clinically.

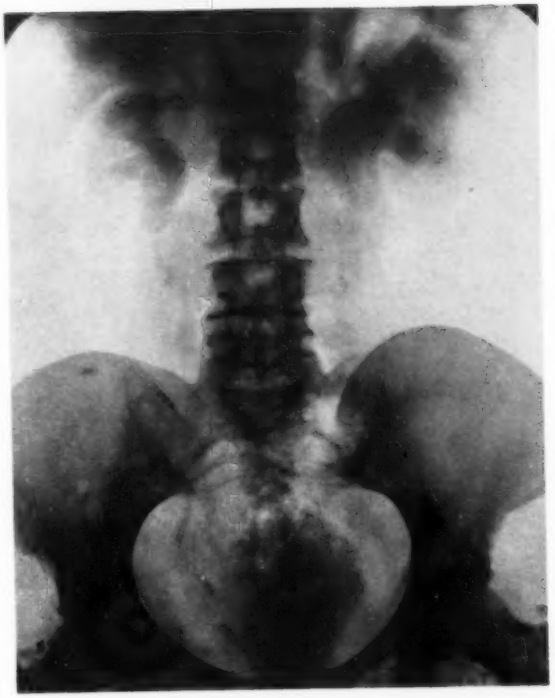

FIG. 7

Radiograph showing bilateral hydronephrosis 10 months after treatment.

bilateral hydronephrosis 10 months after her treatment.

Each of these patients showed an area of radium necrosis in the bladder and since, in this clinic, we now cystoscope every patient who complains of dysuria after treatment, the finding of radium bladder ulcers has become more frequent, so that it seems reasonable to suggest that the routine employment of cystoscopy and pyelography at 6-monthly intervals would help in the early detection of these lesions. Patients showing bladder ulceration should be studied by pyelography at 3-monthly intervals until the lesion in the bladder has healed, as it has been seen in this series that gross changes in the pyelogram can occur very quickly, and thus the opportunity to treat these patients may be lost. Jaffe *et al.* drew attention to this fact in their paper in 1940.

Radiation necrosis appears to be very common in the United States of America, but it should be remembered that in that country there seems to be a tendency to overtreat cases of carcinoma of the cervix by radiotherapeutic measures.

Conclusions

The conclusions to be drawn from this study fall into two parts, namely that concerning the pre-treatment pyelogram and that concerning the use of pyelography in the follow-up of treated cases.

1. *The pre-treatment pyelogram*

An abnormality in the pyelogram of a patient with carcinoma of the cervix is a sign of very grave significance irrespective of the clinical advancement of the tumour, and although these abnormalities tend to be seen more frequently in patients with advanced tumours the frequency with which they are seen in those suffering from clinically less advanced tumours is not inconsiderable.

Such an abnormality almost always indicates interference with the renal tract by extensions of the growth which may not always be apparent clinically.

It would appear that these abnormalities may result from extensions of the tumour into the broad ligament or by involvement of the lymph nodes. This latter event is more frequent than has hitherto been thought. In some cases infiltration of the periureteral lymphatics is the cause of the abnormality. These abnormalities tend to occur more frequently in the more malignant types of tumour and are seldom seen in those which respond favourably to radium. In only 1 patient in all those studied did radium cause a partial reversion to normality in the appearances of the pyelogram, and surgery, limited to Wertheim's hysterectomy, was hardly more successful. In 3 cases extended radical surgery has caused a large hydronephrosis to return to normal. One patient presented with vesico-vaginal fistula which she had had for 6 months. Intravenous pyelogram showed that the right kidney was normal but that the left had considerable hydronephrosis. She was treated by pelvic exenteration during which the right kidney had to be removed. A radiograph taken 6 months later showed that the previously hydronephrotic left kidney had now returned to normal. Unfortunately this patient died shortly afterwards but in the meantime she returned to a way of life which had been completely impossible during the months in which she had been totally incontinent.

It would seem that since the results are so bad in all types of cases when the pyelogram is abnormal, some patients might be considered for pelvic exenteration on the grounds of an abnormal pyelogram when otherwise the clinical extent of the disease would not suggest this procedure. No doubt many cases with extensive lymph node involvement would be found in this group but some at least might be given a chance of survival which they otherwise may not have had.

Finally, if use is to be made of the pyelogram in the follow-up of treated patients, it is essential to have a pre-treatment radiograph for purposes of comparison.

There would seem to be no excuse whatever for treating a patient with carcinoma of the cervix without first studying the urinary tract unless it be the case which is so advanced on clinical grounds and unfit for any treatment, other than palliative radium, that the condition of the urinary tract is only of academic interest.

2. *The Use of the Pyelogram in the Follow-up of Treated Cases*

The use of the pyelogram in this type of case would appear to be twofold. Firstly, and of most practical importance, is the early detection of changes in the urinary tract which may result from radium necrosis. It is obvious that the pyelogram alone cannot tell whether the obstruction is necrotic or neoplastic in origin but, taken in conjunction with clinical and cystoscopic findings, especially in a case where the response to radium has been favourable as judged by the cell count technique, it should clearly indicate when diversion of the urinary tract is indicated and therefore save lives. The death of a patient in such circumstances is nothing short of tragic.

Secondly, it may give early evidence of recurrence, and here again a few of these patients may still be suitable for extended radical surgery. It should also serve as a clear indication that any further radiotherapy is completely contra-indicated, and lastly it may provide a means of arriving at an earlier but definite unfavourable prognosis which, although it does not save the patient's life, may be of some use to her medical attendants who might otherwise be left guessing at the true state of affairs.

I should like to express my thanks to Mr. C. J. L. Thurgar and Mr. S. Way of the Newcastle Regional Cancer Organization, Dr. D. Ramage, Queen Elizabeth Hospital, Gateshead, and Drs. Glucksmann and Cherry, Strangeways Research Laboratory, Cambridge.

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THE HELICOID UTERUS

BY

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THE careful studies of Goerttler (1930) indicate that the uterus is constructed from two spiral systems of muscle bundles, originally the Müllerian ducts and later represented by the musculature of the Fallopian tubes. These two systems sweep caudally in embryonic life and fuse in concentric interlacing circles to form the adult pattern of uterine musculature. The muscle fibres are arranged in bundles which interlace in a basket-weave pattern, so complicated as to defy medical illustrators from the time of Vesalius.

One is prone to accept the concept that the two Müllerian ducts meet exactly in the midline by approach in the direct coronal plane of the body and, therefore, that the adult uterus is invariably positioned dead centrally. However, careful examination of X-ray films of cases submitted for hysterosalpingography will show that in a certain proportion the uterus assumes an asymmetrical position.

I was stimulated to find an explanation for this X-ray phenomenon because I observed that it presented entirely in women attending the infertility clinic. Of 3,145 women who attended the infertility clinic during the years 1946 to 1950 inclusive, 48 or 1.5 per cent were shown to have their uteri situated in an asymmetrical position. I re-examined these cases under anaesthesia and was able to confirm, bi-manually, the deviation of the uterine body to the side indicated in the X-ray film. All mechanical causes for the deviation in the X-ray picture could be excluded—the bladder and rectum were emptied before exposure, and in several cases, to exclude a possible deviation by the intra-uterine nozzle used to introduce the lipiodol, the nozzle was removed and the oil prevented from escaping by gripping the cervix in the region of the external os with a modified tongue forceps.

When I was convinced that this peculiar deviation was protean in type and a possible inherent peculiarity of the uterine musculature I decided to investigate further, especially with regard to its incidence in the adult female and in female infants, and its relationship to infertility.

The study covered a 5-year period, 1946 to 1950 inclusive, and was carried out on two lines:

(1) Investigation of all types of anomalies of the female genitalia, including the deviated uterus, diagnosed in gynaecological patients seen at the Kandang Kerbau Hospital, Singapore.

(2) Postmortem investigation of the external and internal female genitalia of all stillbirths and perinatal deaths occurring in female babies.

Strangely, the female genital organs have been neglected in the study of congenital foetal abnormalities, and I have not been able to trace any worthy publication of work on this subject.

TABLE I
Showing the number of new patients seen at the Gynaecological Department

	In-patients	Out-patients	Genital anomalies
1946 ...	1,304	1,373	9
1947 ...	1,704	2,616	20
1948 ...	1,846	4,166	25
1949 ...	2,101	5,875	32
1950 ...	2,494	6,247	48
Total	9,449	20,277	134
	Grand total	29,726	

The total number of anomalies of the female genitalia seen in these 29,726 patients was 134 cases, almost all of which were confirmed by me. This makes the incidence about 0.5 per cent or 1 in 222 cases. Many of the 134 patients exhibited 2 or more anomalies, but Table II records the main anomaly in each case.

TABLE II

	No. of cases	Remarks
Vulva		
(a) Pseudohermaphroditism	1	Urethra opened on anterior vaginal wall well within introitus.
(b) Fusion of labia minora	3	All in young children, probably an acquired defect.
(c) Imperforate hymen	5	
Vagina		
(a) Congenital recto-vaginal fistula and absence of anal orifice	2	Due to persistence of the urorectal septum and anal plate.
(b) Short posterior wall with shallow dome	11	This anomaly occasionally co-exists with a definite uterine anomaly.
(c) Constriction of vaginal canal at junction of lower 1/5 and upper 4/5	8	Site of constriction marks the junction of the sino-vaginal bulb with the Müllerian ducts.
Cervix		
Small, button, conical, cauliflower, or with hexagonal-like margin	10	This anomaly often indicates a co-existing anomaly of the uterine body. The total number recorded was 39; the remaining 29 co-existed with a definite anomaly of the uterine body.
Uterus		
"Helicoid" or spirally asymmetrical	48	This anomaly will be commented upon in detail later in the text.
Tubes		
Long, tenuous and tortuous	6	Seen in lipiodolograms. All showed spasm to oil.
Ovaries		
Round, small and hard, or "pencil-shaped"	13	Eight of these anomalies were proved at subsequent laparotomy.
Gross Anomalies		
(a) Absence of vagina and uterus	5	
(b) Congenital atresia of upper 4/5ths of the vagina	2	
(c) Uterus bicorpus bicollis	5	Double vagina present in 3 cases.
(d) Uterus bicorpus unicollis	3	Single vagina in all cases.
(e) Uterus unicorpus	1	Proved by X-ray and laparotomy.
(f) Uterus septus	6	Both types discovered during D. and C. operation.
(g) Uterus subseptus	3	
(h) Rudimentary horn	2	Both discovered at operation, 1 ruptured at 10 weeks pregnancy, and the other at 22 weeks pregnancy.
Total	134	

The commonest anomaly as shown in Table II is the spirally asymmetrical uterus. This type of uterus shall hereinafter be called the "Helicoid Uterus", and the reason for the choice of the adjective "helicoid" and the nature of the spiral twist will be discussed later in this paper.

This helicoid uterus is often missed in a bimanual examination unless one is constantly on the look-out for it, especially in cases of infertility.

Of the 48 cases of helicoid uteri, 35 were examined under general anaesthesia after emptying bladder and rectum, 22 cases were examined radiologically, and 3 of the latter cases were submitted to laparotomy and the anomaly confirmed.

The Examination under General Anaesthesia

The main features disclosed in this examination were:

(*a*) The obvious deviation of the uterus to one or other side of the midline. One half of the uterus appeared to lie more anterior than the other half.

(*b*) The side on which the deviation was recognized indicated, without exception, the side

FIG. 1 *Case* 6

Hysterosalpingogram showing deviation of helicoid uterus to left and apparent forward twist of left horn.

FIG. 2 *Case* 7

Hysterosalpingogram showing deviation of helicoid uterus to left. This case was submitted to laparotomy, when it was proved that the left half of the uterus was twisted anteriorly and better developed than the right.

FIG. 3 *Case* 9

Hysterosalpingogram showing deviation of helicoid uterus to right. This case was submitted to laparotomy which proved the right half of the uterus to be spirally twisted anteriorly and better developed than the left.

FIG. 4 *Case* 10

Hysterosalpingogram showing deviation of helicoid uterus to the right. At laparotomy the separation of the two halves of the uterus was more marked than in the usual case of helicoid uterus, and the right horn was better developed than the left.

FIG. 5 P.M. 11
Helicoid uterus. Larger right half twisted anteriorly.

FIG. 6 P.M. 32
Helicoid uterus. Larger right half twisted anteriorly, with deviation to right.

FIG. 7 P.M. 77

Helicoid uterus. Right half larger than left, twisted anteriorly, with deviation to right.

FIG. 8 P.M. 107

Helicoid uterus. Left half larger than right, with anterior twisting. Right tube undeveloped. Left ovary "pencil-shaped."

of the uterus which was the better developed anatomically.

(*c*) The uterine sound when passed met with a resistance just at the anatomical site of the internal os, but it entered easily into the uterine cavity when it was guided in the direction of the deviated uterine body.

(*d*) In 8 cases a partial septum could be felt with the sound. The anomaly would have been missed if one had not been alert to this possibility.

The Incidence and the Types of the Female Genitalia seen at Postmortem of Stillbirths and Perinatal Deaths of Female Babies

The relatively high incidence of helicoid uteri discovered clinically prompted me to pursue further the study of this anomaly by postmortem examination of the uteri of all available female foetuses.

The postmortems were performed chiefly with a view to a study of the uteri, and the presence of concomitant anomalies in other organs, especially the urinary system. The uterus was examined *in situ* to note its symmetry and position in the pelvic cavity, and then dissected away together with the vagina, bladder and rectum to be further examined in detail and photographed.

It was found that 54 or 6.7 per cent of uteri so examined presented major or minor anomalies of fusion of the Müllerian ducts, and in some there were anomalies of the tubes, or ovaries.

The types of the 54 anomalies of the genitalia may be grouped as follows:

Helicoid uterus the only anomaly found	44
Helicoid uterus and giant ovaries	2
Helicoid uterus, pencil-shaped right ovary and undeveloped right tube	1
Helicoid uterus and pencil-shaped right ovary	1
Helicoid uterus and rounded right ovary	1
Helicoid uterus, undeveloped right tube and ovary	1
Helicoid uterus and undeveloped right ovary	1
Uterus unicornis	1
Uterus unicornis and pyramidal right ovary	1
Absence of uterus	1
Total	54

TABLE III

Showing the total number of stillbirths and neonatal deaths of female foetuses and the number of postmortems

	1946	1947	1948	1949	1950	Total
Number of female stillbirths	127	123	172	190	208	820
Number of female neonatal deaths	81	86	83	112	142	504
Total	208	209	255	302	350	1324
Number of postmortems	94	101	165	213	230	803

The Incidence of Pregnancy in the 48 Infertile Patients with the Helicoid Type of Uterus

In the case of 14 of these patients it was found that the husband was either azoöspermic or definitely oligospermic, and, therefore, they were not treated from the point of view of their infertility.

Of the remaining 34 patients, 32 were treated by utero-tubal insufflation, including 22 who also had lipiodologram examinations. Of these patients only 4 or 11.8 per cent subsequently became pregnant in the follow-up examinations to date (October 1952). This figure of success rate is 3 times lower than that obtained in the follow-up of a control series of patients.

The Radiological Examination

Hysterosalpingography was resorted to in 22 cases of suspected helicoid uterus. In every case the rectum was emptied by enema, and the bladder by catheterization, just before injection of the lipiodol. Possible deviation of the uterus by the intra-cervical nozzle was excluded by removal of the nozzle and gripping the cervix in the region of the external os with a modified tongue forceps.

Concomitant congenital anomalies in other organs were found in 12 cases or 22.2 per cent of the 54 cases studied. Of all concomitant anomalies, 5 or about 10 per cent involved the urinary system.

These extra-genital congenital abnormalities were:

Exstrophy of bladder and absence of right kidney and ureter	1 case
Horse-shoe kidney	1 case
Double ureter	1 case
Partial double right ureter	1 case
Absent left kidney	1 case
Hydrocephalus	1 case
Cleft palate	1 case
Obliteration of bile-ducts	1 case
Atresia of small intestine	1 case
Recto-vaginal fistula (vulvo-vaginal anus)	1 case
Imperforate anus	2 cases

In the remaining 749 postmortems, that is, those in which the genital organs were normal, there were altogether 42 extra-genital abnormalities, i.e. 5.6 per cent. It is thus seen that extra-genital abnormality was 4 times more common in cases with genital anomaly than in those without such anomaly.

The classification of the 42 extra-genital abnormalities found in the 749 foetuses with a normal genital tract was as follows:

Hydrocephalus	2	Imperforate anus	5
Anencephalus	1	Exomphalus	3
Microcephalus	1	Congenital heart disease	11
Cleft palate	2	Syndactyly	1
Cleft palate and hare lip	2	Exstrophy of bladder	1
Atresia of small intestine	1	Horse-shoe kidney	1
Atresia of large intestine	1	Obliteration of bile ducts	2
Atresia of oesophagus	2	Talipes equino varus	1
Duodenal obstruction	2	Talipes equino valgus	1
		Spina bifida	2

The idea that the two Müllerian ducts meet in a straight line mesially is erroneous, for, in my study, in 6.7 per cent of 803 postmortem examinations of the foetus this was found not to be so. Even in the case of the uterus arcuatus or cordiformis the notch indicating the two halves was not found to be in the meridian in a single case studied. The term "asymmetrical uterus" has been used by several writers for this type of anomalous development of the uterus, but, in my opinion, the term is inadequate to define, and is not descriptive of, the fabric of the body of the uterus.

This type of asymmetrical uterus is not to be confused with Rudolph's description (1940) of pseudo uterus arcuatus caused by a temporary inco-ordination of the uterus leading to functional malformations. He refers to "changes in contour, in the normal and parturient uterus" and goes on to say that "a disturbance of the physiology of the pregnant and parturient uterus may lead to differences in tone and strength of contraction of each lateral half of the uterus which would result in asymmetry".

I shall try to explain, by invoking the aid of geometrical and mechanical principles, the morphological peculiarity which results in anomalies in the shape of the uterus. Starting with our own stock-in-trade of knowledge, it is axiomatic that shape or form is the resultant of forces, and the form of an organ is "a diagram of forces". The elementary concept of form as determined by varying rates of growth was clearly apprehended in the mathematical mind of Haller (1760). Every part of a growing organ has its own specific rate of growth referred to this or that particular direction and it is by the ratio between these rates in different directions that we must account for the external form of all organs. This ratio may be of a simple kind, as in the mathematically definable outline of a shell and the smooth curve of the margin of a leaf, or complex, as in the human organism, where growth tends not to be uniform in all directions nor have we reason to expect it should. Within the growing system of the human body all manner of structural differences come into play and set up unequal resistance of growth in one direction or another resulting in heterogeneous development.

The mathematical principle of geodesics (or geodetics) can explain the conformation of a certain class of shells. A beautiful geodesic of the circular cone is exemplified in the structural line of a spiral shell, the Turritella.

This spiral, or rather helical, geodesic is particularly common in cylindrical structures, and this principle may be applied to the uterus which develops by fusion of two cylindrical

FIG. 9 P.M. 139

Helicoid uterus. Right half larger than left, and twisted anteriorly. Slight deviation to right.

FIG. 10 P.M. 220

Helicoid uterus. Resembles uterus arcuatus, but larger left half twisted anteriorly, and left half of fundus higher than right.

FIG. 11 P.M. 268

Helicoid uterus. Large right half twisted anteriorly, and right half of fundus higher than left. Rounded right ovary.

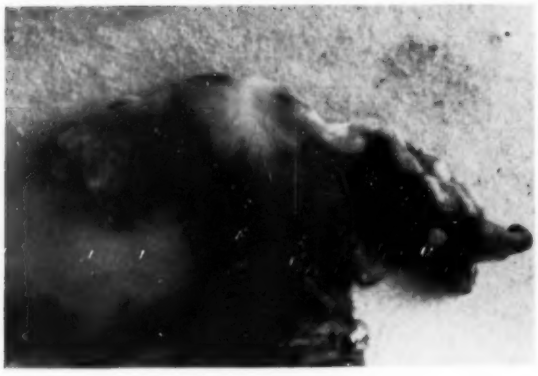

FIG. 12 P.M. 413

Helicoid uterus. Larger right half twisted anteriorly, with deviation to right.

FIG. 13 P.M. 847

Helicoid uterus. Larger left horn twisted anteriorly, and left half of fundus higher than right. Torsion to right unusual.

FIG. 14 P.M. 601

Helicoid uterus. Resembles uterus arcuatus, but right half larger than left, and twisted anteriorly.

FIG. 15. P.M. 619

Helicoid uterus. Right half larger than left, twisted anteriorly, with slight deviation to right.

FIG. 16 P.M. 746

Helicoid uterus. Larger left half twisted anteriorly, with deviation to left.

FIG. 17 P.M. 756

Helicoid uterus. Resembles uterus arcuatus. Larger right half twisted anteriorly, with deviation to right.

Müllerian ducts. That this principle of the helical geodesic operates in the case of the uterus is shown by the arrangement of the muscular fibres on the surface. As in the case of the stomach and heart, this spiral arrangement of the muscle fibres in the uterus is to be expected from the point of view of mechanical efficiency of the uterus as a hollow muscular organ designed to expel the products of conception. For if we imagine a contractile fibre to be fixed by its two ends upon a curved surface, it is obvious that its first effort of contraction will tend to expend itself accommodating the fibre to the form of the surface. This " stretching it tight " results in its assuming a direction which is the shortest possible line upon the surface between the two extremes. It is only then that further contraction will have the effect of constricting the tube and so exercising pressure on its contents. Thus the muscular fibres, as they wind over the curved surface of the uterus, arrange themselves anatomically in geodesic curves. It is as a simple, necessary result of geodesic principles that we see these figures-of-eight produced to which in the case, for instance, of the heart muscles, Pettigrew and other anatomists have ascribed peculiar importance.

In the primitive undisturbed cylinder, as in an artery or in the intestines (Carey, 1921; Lewis, 1922), the muscles run in simple geodesic lines and constitute the circular and longitudinal coats which form the normal musculature of all tubular organs. In the uterus the musculature consists, in great part, of the original simple system of circular and longitudinal muscles which enveloped the original tubes; which tubes, after a process of local thickening, expansion and especially twisting, come together to constitute the composite human uterus. The muscle fibres still run their shortest possible course from start to finish over the complicated curved surface of the uterus.

Carrying this geodesic principle of development of the uterus from two simple cylindrical tubes still farther, it is rational to assume that varying degrees of dilatation and of twisting may be exerted on one or both cylinders, after the fashion of the glass-blower. A cylinder is especially resistant to torsion, but is very easily flexed, and this is particularly evident in the flexed or retroflexed position of the uterine body.

The spiral twist in the horn of horned quadrupeds is due to inequalities in rate of growth of the growing stem and complete radial symmetry does not often occur. The radial anomalies may be such as arise intrinsically from structural peculiarities in the stem itself, or externally to it by reason of unequal or various localized forces.

In the twining stem of a climbing plant the same principle applies, but in this case the twist is due to differing rates of growth on either side of the advancing stem (Darwin, 1865, 1880).

It is reasonable to conclude that the explanation for the spiral twist and asymmetry in the helicoid uterus lies in the inequality in the rate of growth of the two Müllerian ducts, for in this type of uterus one half is better developed than the other, and this better-developed portion is invariably anterior to the other. The word " helicoid ", therefore, seems to be the appropriate adjective to designate this type of uterine anomaly. Besides this spiral twisting on the longitudinal axis, there is also in this morphological anomaly of the uterus an element of deviation, either an exaggeration of anteversion or retroflexion or a lateral deviation.

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THE BLOOD-PRESSURE IN TOXAEMIA OF PREGNANCY*

I. Spontaneous Diurnal Variability

BY

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ELEVATION of the arterial blood-pressure constitutes one of the most important symptoms of toxaemia of pregnancy. Since 1946 most of the cases with toxaemia of pregnancy referred to St. Erik's Hospital have been thoroughly studied regarding blood-pressure, renal function, plasma volume, cardiac output, and other functions of haemodynamic interest. This report is concerned with the spontaneous variability of the arterial blood-pressure in a fraction of those cases.

MATERIAL AND METHODS

The present analysis was carried out in 108 cases of toxaemia of pregnancy diagnosed according to current standards. All had varying amount of protein in the urine. The proteinuria persisted until delivery or longer. Only cases where the blood-pressure on two or more occasions was 160/100 mm.Hg or higher or who had definite hypertensive eye-ground changes are included. In some of the cases the blood-pressure was known to be normal before pregnancy, but in most cases the height of the pre-pregnant blood-pressure was unknown. Some patients with undiagnosed hypertensive cardiovascular disease (HCVD) may be included in the present material as the blood-pressure even in such cases may be normal during early pregnancy. Patients with glomerulonephritis, pyelonephritis, or known HCVD are excluded from the present study.

The blood-pressure was determined with the auscultatory method on the arm using a cuff and a von Recklinghausen tonometer. The tonometer was repeatedly calibrated against a mercury manometer. Readings were made every 2 hours during a 24-hour period as described by Hammarström (1947). Usually this 24-hour reading was made on the first or second day of the patient's stay in the hospital. In some patients the progress of the disease was followed with repeated 24-hour readings. Only the first is included in the present analysis. The patients were usually referred to the hospital within the first or second week after they developed symptoms of toxaemia of pregnancy. All blood-pressure determinations used in the present analysis were thus made within 2 weeks after the development of symptoms.

The eye-grounds were studied by a consultant ophthalmologist and grouped according to Wagener and Keith (1939).†

The material is grouped in the same groups as used by Hammarström (1947) according to the eye-ground changes. Group 1 comprises the cases without eye-ground changes (31 cases), Group 2 those with only vascular changes, arteriosclerotic or spastic (Groups I and II of Wagener and Keith) (71 cases), and Group 3 those with hypertensive retinopathy (Groups III and IV of Wagener and Keith) (6 cases).

The material is also divided according to the extent of proteinuria, one group with less than 1 pro mille proteinuria and the other with greater protein excretion.

The number of cases in the different groups and age distribution is shown in Table I. The mean age was about the same in all groups.

In Table II the material is grouped according to the length of pregnancy when studied. The earlier the symptoms of toxaemia developed the older were the patients.

The results of the 24-hour blood-pressure determinations were treated statistically with

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† The authors want to express their thanks to Dr. G. von Bahr, who examined most of the cases in the present study.

TABLE I

Number of cases in different groups and age distribution

Group	15–19	20–24	25–29	30–34	35–39	40 —	Mean
1	1	3	9	9	8	1	30.8
2	2	10	20	17	12	10	30.8
3	0	1	3	1	1	0	29.3
≤1	2	4	14	15	12	9	32.2
>1	1	10	18	12	9	2	29.8

analysis of variance according to Fisher (1936) (Bonnier and Tedin, 1940). The results of this analysis are compared with Hammarström's results (1947). His material consisted of patients with HCVD. For comparison only his results in women (118 cases) have been used. His 118 cases consisted of 23 in Group 1, 78 in Group 2, and 17 in Group 3. He had thus slightly more cases in Groups 2 and 3 and fewer in Group 1 than in the present material.

TABLE II

Mean age and mean blood-pressure of cases distributed according to length of pregnancy when studied

Months of pregnancy	Cases	Age (mean)	Mean blood-pressure
1–6	12	34.3	144.6/90.0
7–8	30	30.8	154.2/103.8
9–10	66	28.3	146.7/98.3

RESULTS

In Table III the mean height of the blood-pressure in our material is tabulated. For comparison the mean blood-pressure in Hammarström's material is also listed. The difference between the height of the blood-pressure in the different groups in the toxaemia material is statistically significant but small, much smaller than in the HCVD material. It is of interest that in Group 1, without eye-ground changes, the diastolic blood-pressure is higher in the toxaemia cases than in the cases with HCVD. In the other groups the blood-pressure in toxaemia is considerably lower than in HCVD.

The cases with proteinuria less than 1 pro mille have significantly lower mean blood-pressure than in the cases with higher protein excretion (Table IV). This table also gives the values of the mean blood-pressures for the different groups, distributed according to eye-ground changes. For comparison the values in Hammarström's HCVD material are also given. As is seen in Table V there is a statistically significant difference between means of 24-hour readings in the different groups.

The variability of the blood-pressure in the different groups is demonstrated in Table VI. The mean square "within patients" expresses in figures this variability. Hammarström's comparable figures are listed within brackets. The variability of the blood-pressure in our material is consistently less than in Hammarström's. This is most pronounced in Group 2 with a systolic

TABLE III

Means of highest and lowest blood-pressure during 24-hour readings in 108 cases distributed according to eye-ground changes. Within brackets values from Hammarström's HCVD material

Group	Blood-pressure	Spontaneous readings		
		Highest	Lowest	Variation
1	Systolic	166 (186)	133 (131)	33 (55)
	Diastolic	112 (108)	87 (80)	25 (28)
2	Systolic	167 (233)	133 (167)	34 (66)
	Diastolic	111 (136)	89 (104)	22 (32)
3	Systolic	182 (270)	138 (202)	44 (68)
	Diastolic	116 (154)	92 (119)	24 (35)

mean square of 124 as compared with 289 and a diastolic of 56 as compared with 199. The variability of the systolic blood-pressure in Group 3 is more marked with almost the same mean square as in the cases with HCVD. The diastolic blood-pressure on the contrary showed the same variability as in the toxaemia Group 2.

When the material is divided according to the renal excretion of protein, the variability of the systolic blood-pressure is less in the group with lower proteinuria than in the other group. The diastolic pressure, on the contrary, shows less variability in the group with greater protein-excretion than in the first group. The quotient pulse pressure/diastolic pressure is the same in all groups (Table IV).

Discussion

Hammarström in 1947 studied the variability of the arterial blood-pressure in patients with HCVD at the same department as that in which our patients have been hospitalized. For that purpose the blood-pressure was determined every other hour during a 24-hour period. The material was divided into 3 groups according to the eye-ground changes and treated statistically with analysis of variance. He demonstrated a positive correlation between the degree of eye-ground changes and the height of the blood-pressure. He further showed that there was a greater 24-hour variability in the patients with more pronounced eye-ground changes than in those without or with less marked eye-ground changes. The cases with more advanced HCVD and higher blood-pressure had thus greater variation in the blood-pressure than those with lower blood-pressure.

The present study was done in order to compare the blood-pressure elevation during toxaemia of pregnancy with the blood-pressure in HCVD. The material was arranged in the same groups and the material was selected according to the same blood-pressure standards as those used by Hammarström, in order to make it possible to use his material as representative for the blood-pressure in HCVD. The blood-pressure readings used in this study were furthermore made exactly as in Hammarström's and by the same persons. The eye-grounds were also classified by the same ophthalmologist. The blood-pressures reported here are thus fully comparable with those earlier reported by Hammarström.

Several authors have suggested that the blood-pressure is regulated in some other way during pregnancy than in the non-pregnant state. Brust, Assali, and Ferris (1948) have studied the response of the blood-pressure to tetraethylammonium during pregnancy. They found marked differences in the response during normal and toxaemic pregnancy and concluded that the blood-pressure is regulated during pregnancy by a nervous mechanism instead of the normal humoral regulation. In toxaemia of pregnancy, however, the blood-pressure according to Brust and co-workers is more controlled by humoral factors than by sympathetic tone.

The present study also demonstrates a difference in the behaviour of the blood-pressure during toxaemia of pregnancy as compared with non-pregnant cases with HCVD. The mean blood-pressure values in the toxaemia groups are considerably lower than in the corresponding groups of HCVD, except in the group with normal eye-grounds. It is remarkable that in toxaemia of pregnancy eye-ground changes grade III (Group 3) occur with a blood-pressure of only 157/104 as daily mean. In the cases with HCVD similar eye-ground changes were recorded in patients with a mean blood-pressure of 230/134. This is the case, though the toxaemia cases are much younger than those with HCVD. Older age can thus not be the reason for the more advanced eye-ground changes. One possible explanation for this would be if the cases in Group 3 earlier had advanced HCVD and that during pregnancy the blood-pressure had decreased. The subsequent course of these patients speaks against this. Toxaemia thus tends to produce pronounced eye-ground changes at blood-pressure levels that are considerably lower than those in cases of HCVD with similar eye changes. On the other hand almost 30 per cent of the toxaemia cases had completely normal eye-grounds. The blood-pressure in those cases was a fraction lower than in those with eye-ground changes. The diastolic pressure was, however, higher than in the cases with HCVD though not as high as in the HCVD Group 2.

In the toxaemia cases the difference in blood-pressure between the groups was small. The

TABLE IV

Means of 24-hour readings in 108 cases distributed according to eye-ground changes and degree of proteinuria. For each group is also given the pulse pressure/diastolic blood-pressure ratio. For comparison corresponding values from Hammarström's HCVD material.

Group	Blood-pressure	Number of cases	Readings	Blood-pressure mean mm. Hg	Hammarström
1	Systolic	31	363	147.4	148
	Diastolic			98.4	92
	Pulse pressure / diastolic			0.50	0.61
2	Systolic	71	831	149.0	189
	Diastolic			99.2	114
	Pulse pressure / diastolic			0.52	0.66
3	Systolic	6	70	156.9	230
	Diastolic			104.0	134
	Pulse pressure / diastolic			0.51	0.71
Albumin <1/1,000	Systolic	56	656	144.4	
	Diastolic			95.4	
	Pulse pressure / diastolic			0.51	
Albumin >1/1,000	Systolic	52	608	153.9	
	Diastolic			103.4	
	Pulse pressure / diastolic			0.49	

TABLE V

Variability of blood-pressure in 24-hour readings in 108 cases distributed according to variability between groups, divided according to eye-ground changes and degree of proteinuria

Comparison	Variance	Degrees of freedom	Systolic pressure		Diastolic pressure	
			Sum of squares	Mean square	Sum of squares	Mean square
Between groups according to eye-ground changes	Between groups	2	5286	2643	1866	933
	Within groups	1261	440313	349	228484	181
	Total	1263	445599	P<0.001	230350	P<0.001
Between groups according to albuminuria	Between groups	1	28595	28595	20597	20597
	Within groups	1262	417004	330	209753	166
	Total	1263	445599	P<0.001	230350	P<0.001

TABLE VI

Variability of blood-pressure in 24-hour readings in 108 cases, distributed according to variability between and within patients, grouped according to eye-ground changes and degree of proteinuria. Within brackets values from Hammarström's HCVD material

Group	Variance	Degrees of freedom	Systolic pressure		Diastolic pressure	
			Sum of squares	Mean square	Sum of squares	Mean square
1	Between patients	30 (22)	63423	2116 (5371)	50413	1680 (1251)
	Within patients	332 (270)	44695	134 (162)	26883	80 (81)
	Total	362 (292)	108118	299 (555)	77296	213 (169)
2	Between patients	70 (77)	208393	2977 (1116)	98363	1405 (2433)
	Within patients	760 (903)	94837	124 (289)	42910	56 (199)
	Total	830 (980)	303230	365 (1143)	141273	170 (375)
3	Between patients	5 (16)	11918	2384 (6493)	5937	1187 (3281)
	Within patients	64 (199)	17047	266 (289)	3958	61 (107)
	Total	69 (215)	28965	420 (751)	9895	143 (343)
Albuminuria <1	Between patients	55	155042	2819	96891	1762
	Within patients	600	68400	114	42446	70
	Total	655	223442	341	139337	213
Albuminuria >1	Between patients	51	105383	2066	39091	766
	Within patients	556	88379	158	31325	56
	Total	607	193762	319	70416	116

cases in Groups 2 and 3 usually had more symptoms than the cases in Group 1. This was, however, not always true. The present differentiation of the material after the eye-ground changes does not parallel the clinical differentiation in severe or mild pre-eclampsia. Some of the cases in Group 2 seemed to have the same severity of the disease as the cases in Group 3, except for the eye-ground changes. In these severe cases examination of the eye-grounds was of some value for assessing the severity of the disease, but in most other cases the eye-ground findings did not contribute to the general clinical evaluation of the patient.

When the material was divided after the protein excretion it was found that there was a certain degree of parallelism between the blood-pressure levels and the proteinura. This is typical of toxaemia of pregnancy, in contrast to HCVD.

The diurnal variability of the blood-pressure was consistently less in the toxaemia cases than in the cases with HCVD. This was most pronounced for the diastolic blood-pressure in Groups 2 and 3. The systolic blood-pressure in Group 2 also showed less variability in toxaemia than in HCVD. This difference may be due to the lower level of blood-pressure in toxaemia. That this is not the sole reason for the different variation is shown by the fact that the mean square of the diastolic pressure in our Group 2 is smaller than that of Hammarström's Group 1, though the mean pressure is higher. There is, furthermore, no parallelism between the variability and the mean height of the blood-pressures in the toxaemia material. The diastolic blood-pressure in most cases of toxaemia of pregnancy is thus more fixed than in HCVD. The constancy of the quotient pulse pressure/diastolic blood-pressure also differs in the toxaemia cases as compared to the cases with HCVD. Increased pulse pressure (due to increased systolic discharge of blood?) is not characteristic of toxaemia of pregnancy.

It is of interest to note that, though the diastolic pressure in Group 3 shows the same variability as the diastolic in Group 2, the systolic pressure has greater variability,

approaching that of the cases of HCVD with a considerably higher mean systolic pressure.

The different spontaneous behaviour of the blood-pressure as compared with HCVD points to a different aetiology. In this connexion it is of interest that Hammartsröm did not find any difference in variability of blood-pressure in HCVD and in chronic nephritis. Toxaemia of pregnancy in this respect seems to occupy a unique position. Whether this is due to a humoral regulating mechanism as proposed by Brust and co-workers or to some other reason cannot yet be decided.

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THE BLOOD-PRESSURE IN TOXAEMIA OF PREGNANCY*

II. Influence of Hypotensive Drugs

BY

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IN a previous publication it was demonstrated that the blood-pressure in toxaemia showed less spontaneous variation than in cases with hypertensive cardiovascular disease (HCVD) (Werkö and Brody, 1953). In order to gain more extensive information the reaction of the blood-pressure to a series of different hypotensive drugs was studied. Similar studies have been published by Brust, Assali and Ferris (1948), Assali, Kistner and Garber (1948), Assali, Brust, Garber and Ferris (1950), Assali and Prystowski (1950 a, b), Assali, Vergon, Tada and Garber (1952). The present report compares the blood-pressure-lowering effect of sodium amytal, sodium nitrite, tetraethylammonium-bromide (TEA), dihydroergocornine (DHO) and veratrone in cases of toxaemia of pregnancy. The effect of the drugs on the blood-pressure is also compared with the spontaneous 24-hour variability.

MATERIAL AND METHODS

The study was carried out in 49 cases of toxaemia of pregnancy, diagnosed according to current standards. All had proteinuria that persisted until delivery or longer. Only cases where the blood-pressure on two or more occasions was 160/100 or higher, or who had definite hypertensive eye-grounds, were included in the present analysis. Patients with glomerulonephritis, pyelonephritis, or known hypertensive cardiovascular disease were excluded. The patients had usually been in the hospital 1 to 2 days, and on a salt-poor diet when the tests were started. These were carried out on 3 to 4 consecutive days.

All tests were done with the patient recumbent after a complete rest for at least 1 hour. Before the administration of a drug blood-pressures and pulse-rate were constant for at least 5 minutes. The blood-pressure was determined with the auscultatory method using an arm-cuff and a von Recklinghausen tonometer calibrated against a mercury manometer.

Amytal test was carried out in 39 cases; 0.2 g. sodium amytal was given 3 times by mouth every half-hour. The blood-pressure was recorded every half-hour during 3 hours.

Nitrite test was performed in 8 cases; 0.032 g. sodium nitrite was given by mouth every half-hour in 6 doses. The blood-pressure was recorded during 3 hours.

DHO test was done in 13 cases; 1 mg. DHO was given intramuscularly. Pulse-rate and blood-pressure were determined every 5 minutes for the first half-hour, and every half-hour for 4 hours.

TEA test was carried out in 20 cases; 5 mg. TEA per kg. body weight was given intravenously in 30 seconds (usually between 300 and 450 mg.). Pulse-rate and blood-pressure were determined every minute for 10 minutes and then every 5 minutes for 30 minutes.

Veratrone test was done in 14 cases; 0.5 ml. of veratrone was given intramuscularly. Blood-pressure and pulse-rate were recorded every 10 minutes for 30 minutes and then every half-hour for 6 hours.

The spontaneous variability was determined from a 24-hour blood-pressure reading as earlier described (Werkö and Brody, 1953).

The blood-pressure before the drug was given was compared with the lowest blood-pressure recorded during the influence of the drug. The difference between these pressures is

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designed as the drug-induced lowering of the blood-pressure.

The lowest blood-pressure recorded during each drug test, the " drug floor ", was compared with the lowest blood-pressure recorded during the 24-hour reading.

The eye-grounds were studied by an ophthalmologist* and classified according to Wagener and Keith (1939).

The renal function was studied with clearance techniques, creatinine according to Rehberg (see Smith, 1951) and/or inulin and para-aminohippurate according to Smith (1951).

The material has been subjected to statistical treatment with analysis of variance according to Fisher (1936) and Bonnier and Tedin (1940). The statistical significance is indicated by giving the probability that the values may arise at random.

Results

Table I contains the average lowest blood-pressure for each drug, the maximum, minimum and mean drop in blood-pressure and, for comparison, the lowest blood-pressure during the spontaneous variability 24-hour reading.

TEA showed the most marked blood-pressure reduction. The lowest blood-pressure recorded during TEA effect was 110.8/76.5 on an average, with a mean drop in the systolic blood-pressure of 52.0 mm.Hg. and 31.0 mm.Hg in the diastolic. The maximum drop recorded was 100 mm.Hg for the systolic and 65 for the diastolic blood-pressure. In one case the blood-pressure dropped only from 130/100 to 125/90 mm.Hg.

Veratrone also caused a comparable blood-pressure drop. The lowest blood-pressure was 123.6/77.5 mm.Hg on an average, with a mean drop of 38.2 in the systolic and 30.0 in the diastolic blood-pressure. The maximum drop was 80/80 mm.Hg. and the minimum 15/10 mm.Hg.

DHO decreased the blood-pressure to 129.6/86.2. The mean drop was 19.6 systolic and 11.2 mm.Hg diastolic. The maximum drop was 50/30 mm.Hg. In some cases no change in the blood-pressure was observed. Thus the

* In most cases T. Kornerup, Assistant Professor of Ophthalmology, Karoline Institute, who is thanked for his help.

Table I

Drop in blood-pressure induced by hypotensive drugs and comparison between lowest blood-pressure during different tests and during 24-hour readings.

Test	Blood-pressure	Number of cases	Lowest blood-pressure Mean mm.Hg	Drop in blood-pressure Mean mm.Hg	Maximum drop	Minimum drop	Lowest blood-pressure during 24-hour reading Mean mm.Hg
Etamon		20					
	Systolic		110.8	52.0	100	5	143.3
	Diastolic		76.5	31.0	65	10	94.3
Veratrone		14					
	Systolic		123.6	38.2	80	15	135.7
	Diastolic		77.5	30.0	80	10	91.1
DHO		13					
	Systolic		129.6	19.6	50	0	137.3
	Diastolic		86.2	11.2	30	0	91.5
Amytal		39					
	Systolic		135.4	14.2	50	−10†	136.4
	Diastolic		92.4	8.2	35	−10†	90.1
Nitrite		8					
	Systolic		135.6	16.2	20	10	145.0
	Diastolic		95.6	13.8	20	5	98.5

† Indicates an increase.

influence was considerably less than in the first two drugs.

The least influence on the blood-pressure was exerted by amytal and sodium nitrite. Sodium amytal caused an average decrease of the blood-pressure to 135.4/92.4 mm.Hg, with a mean reduction of 14.2/8.5 mm.Hg. The maximal effect was a decrease of 50/35 mm.Hg, while in 4 instances a slight increase in blood-pressure was recorded. Sodium nitrite decreased the pressure to 135.6/95.6 mm.Hg. The average decrease was 16.2/13.8 mm.Hg. The maximal reduction noted after sodium nitrite was 20/20 with a minimal change of 10/5 mm.Hg.

Table II shows the results of the statistical analysis of the comparison of the influence of the various drugs. A comparison is made both of the blood-pressure drop and of the lowest

TABLE II

Statistical analysis of blood-pressure reducing effect of hypotensive drugs.

Test	Group	Variance	Degrees of freedom	Systolic pressure		Diastolic pressure	
				Sum of squares	Mean square	Sum of squares	Mean square
Amytal ←→ Nitrite	Comparison between lowest blood-pressure	Between groups	1	403	403	401	401
		Within groups	45	7897	175	6624	147
		Total	46	8300	P>0.05	7025	P>0.05
	Comparison between drop in blood-pressure	Between groups	1	26	26	185	185
		Within groups	45	7715	171	4896	109
		Total	46	7741	P>0.05	5081	P>0.05
Etamon ←→ Veratrone	Comparison between lowest blood-pressure	Between groups	1	1354	1354	39	39
		Within groups	32	16785	524	11962	373
		Total	33	18139	P>0.05	12001	P>0.05
	Comparison between drop in blood-pressure	Between groups	1	1555	1555	10	10
		Within groups	32	17200	537	9230	288
		Total	33	18755	P>0.05	2240	P>0.05
Etamon + Veratrone ←→ Amytal	Comparison between lowest blood-pressure	Between groups	1	8160	8160	4386	4386
		Within groups	71	25804	363	18436	259
		Total	72	33964	P<0.001	22822	P<0.001
	Comparison between drop in blood-pressure	Between groups	1	51273	51273	8902	8902
		Within groups	71	24827	349	13938	196
		Total	72	76106	P<0.001	22840	P<0.001
DHO ←→ Amytal	Comparison between lowest blood-pressure	Between groups	1	324	324	384	384
		Within groups	50	11693	233	8602	172
		Total	51	12017	P>0.05	8986	P>0.05
	Comparison between drop in blood-pressure	Between groups	1	279	279	70	70
		Within groups	50	10001	200	5460	108
		Total	51	10280	P>0.05	5530	P>0.05

value reached. Amytal and nitrite have the same effect. There was also no difference between the effect of amytal and of DHO. Veratrone and TEA statistically had the same blood-pressure-reducing effect. There was a statistically significant difference between TEA and veratrone on the one hand and amytal on the other, both regarding the pressure drop and lowest value reached.

Table III contains the statistical evaluation of the difference between the lowest spontaneous blood-pressure reading and lowest reading after different drugs. The lowest value reached after amytal, nitrite and DHO is statistically the same as the lowest spontaneous pressure.

TEA gave significantly lower systolic and diastolic blood-pressure than the lowest spontaneous. Veratrone gave significantly lower diastolic blood-pressure and probably significantly lower systolic pressure.

In Table IV the pulse-rate changes after DHO, TEA and veratrone are recorded. DHO and veratrone both gave significant reduction of the pulse-rate (7.7 and 19.4) and TEA gave a significant increase in pulse-rate (28 beats min.).

Fig. 1 gives the regression lines for the systolic blood-pressure drop after TEA and veratrone respectively. The statistical significance of the correlation coefficients is $0.05>P>0.01$. This indicates that the blood-pressure drop

TABLE III

Statistical analysis of lowest blood-pressure recorded during different tests and during 24-hour readings.

Group	Variance	Degrees of freedom	Systolic pressure		Diastolic pressure	
			Sum of squares	Mean square	Sum of square	Mean squares
Comparison between lowest blood-pressure during DHO test and 24-hour readings	Between groups	1	37	37	165	165
	Within groups	24	5104	212	4077	169
	Total	25	5141	P>0.05	4242	P>0.05
Comparison between lowest blood-pressure during amytal test and 24-hour readings	Between groups	1	534	534	32	32
	Within groups	76	15916	209	11968	157
	Total	77	16450	P>0.05	12000	P>0.05
Comparison between lowest blood-pressure during etamon test and 24-hour readings	Between groups	1	10522	10522	3151	3151
	Within groups	38	16278	428	10818	284
	Total	39	26800	P<0.001	13969	P<0.01
Comparison between lowest blood-pressure during veratrone test and 24-hour readings	Between groups	1	1033	1033	1290	1290
	Within groups	26	5364	206	4296	165
	Total	27	6397	P<0.05	5586	P<0.01
Comparison between lowest blood-pressure during nitrite test and 24-hour readings	Between groups	1	351	351	38	38
	Within groups	14	3222	230	1910	136
	Total	15	3573	P>0.05	1948	P>0.05
Comparison between highest blood-pressure during cold pressure test and 24-hour readings.	Between groups	1	592	592	184	184
	Within groups	44	14133	321	5391	122
	Total	45	14725	P>0.05	5575	P>0.05

TABLE IV

Pulse-rate changes induced by hypotensive drugs.

Test	Cases	Mean	Mean square	Standard deviation	Error of mean
DHO	10	−7.7	33	5.74	1.81
Etamon	23	28	231	15.2	3.16
Veratrone	14	−19.4	152	12.3	2.57

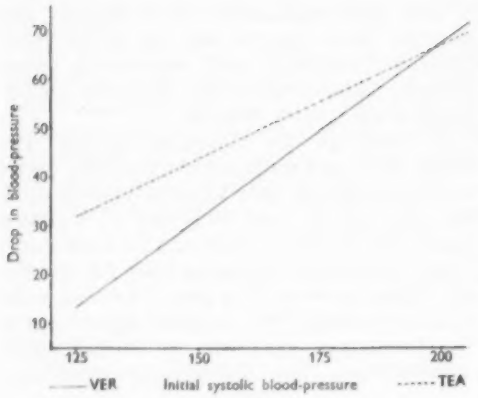

FIG. 1

Correlation between initial systolic blood-pressure and drop in blood-pressure induced by (1) veratrone (——), and (2) TEA (- - - -).
(1) Regression line $y=-78.2+0.73x$.
$\bar{x}=161.7\pm4.40$.
$\bar{y}=38.2\pm5.09$.
Regression coefficient 0.73.
Correlation coefficient 0.63.
$0.05>P>0.01$.
(2) Regression line $y=-26.26+0.47x$.
$\bar{x}=162.7+5.12$.
$\bar{y}=50.2+5.25$.
Regression coefficient 0.47.
Correlation coefficient 0.46.
$0.05>P>0.01$.

induced by TEA and veratrone in this material is a function of the height of the blood-pressure.

Fig. 2 shows the results in some individual cases, showing the varied response to the drugs that were obtained in the same cases.

Fig. 3 shows the result of the TEA test repeated after the patient had been forced to lose weight and oedema fluid by means of salt-free diet, mercurial diuretics, and ammonium chloride. Except for the loss in oedema and weight the signs of toxaemia persisted and the pregnancy terminated spontaneously.

DISCUSSION

The cause of the elevation of the blood-pressure in toxaemia of pregnancy is unknown. The difference in spontaneous behaviour between the blood-pressure in toxaemia and in hypertensive cardiovascular disease suggests that they are influenced and maintained by different causes. The present study was undertaken in order to gain further information regarding the behaviour of the blood-pressure in toxaemia of pregnancy and to assess the therapeutic possibilities of different blood-pressure-lowering drugs.

Sodium amytal has a centrally sedative effect, whereby the blood-pressure is somewhat lowered. In hypertensive cardiovascular disease the lowest blood-pressure after amytal was equal to the lowest spontaneous (Hammarström, 1947). The same was observed in our series of toxaemia of pregnancy. It is of interest that in some cases no blood-pressure reduction was obtained. Sodium amytal can thus depress the central excitability in toxaemia but does not decrease the elevated blood-pressure.

Although sodium nitrite has a peripheral vasodilating action it did not influence the blood-pressure more than sodium amytal. In the few cases where its effect was studied a more uniform response was obtained than with the other drugs. In several cases the blood-pressure showed a reactive increase after the test accompanied by headache and eye symptoms. This caused a discontinuation of the studies with this drug.

DHO also exerted a small decrease in the blood-pressure of the same magnitude as that observed after amytal. DHO has been claimed to have a sympathicolytic action, to counteract epinephrine and to have a central sedative effect. In the present series the blood-pressure drop after DHO seems to be due mostly to the sedative effect, although the small but significant drop in pulse-rate during the influence of the drug suggests some sympathicolytic action. Side-effects in the form of nausea and nasal congestion were noted in several cases in conformity with the experience in cases with hypertensive cardiovascular disease.

Veratrone is a crude preparation of veratrum viride, containing all the alkaloids of the plant. The action of the veratrum alkaloids is complex and not totally clarified. Krayer, Wood and Montes (1943) have shown that there is no direct action on the vessels and consider the main effect to be reflex. They state that the action is excited from receptors in the heart and the pulmonary circulation and via the vagus causes the blood-pressure reduction and the

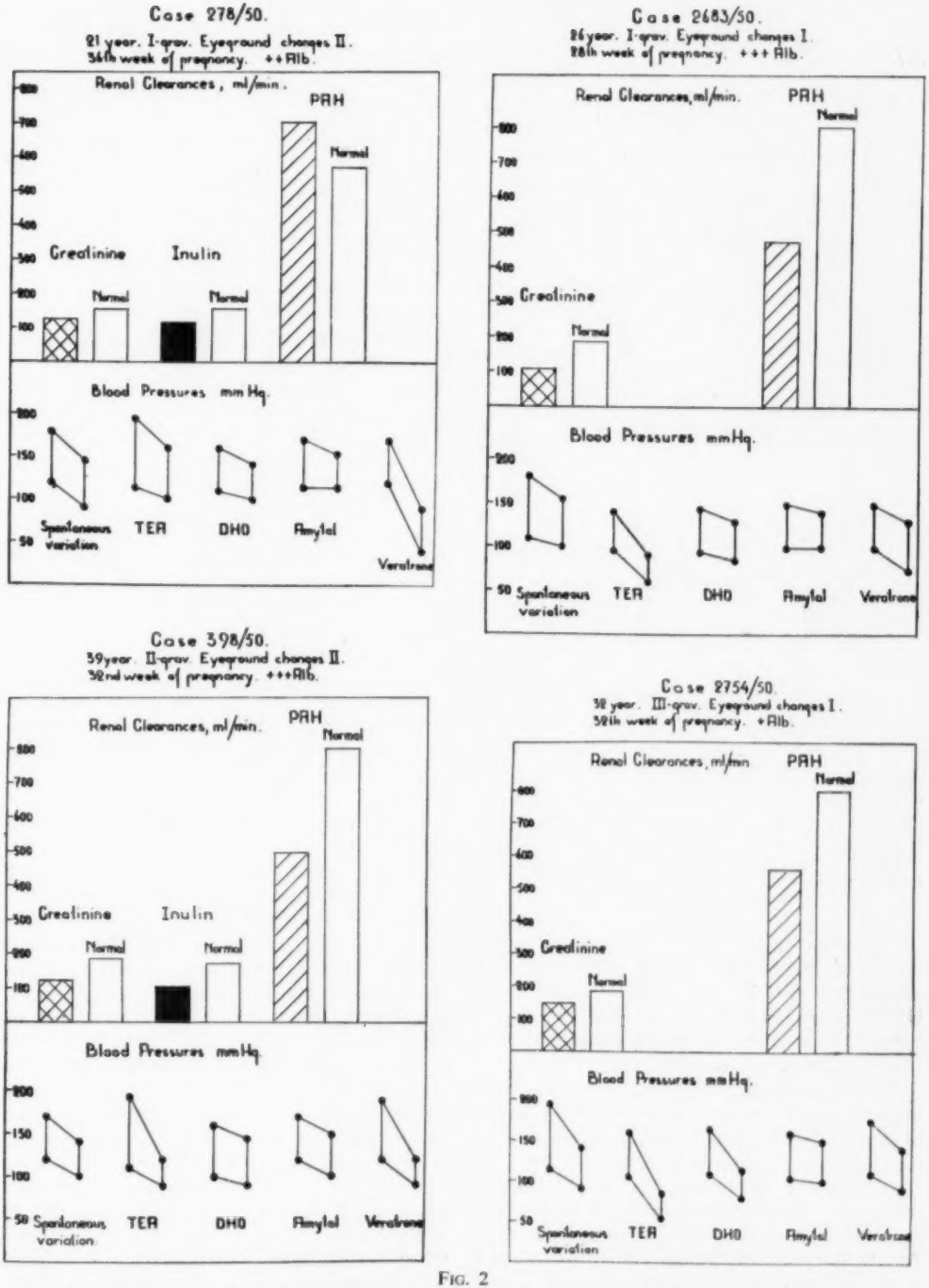

FIG. 2

Spontaneous variability of blood-pressure and reaction to different blood-pressure-lowering drugs, in relation to changes in renal clearances in 4 cases of toxaemia of pregnancy.

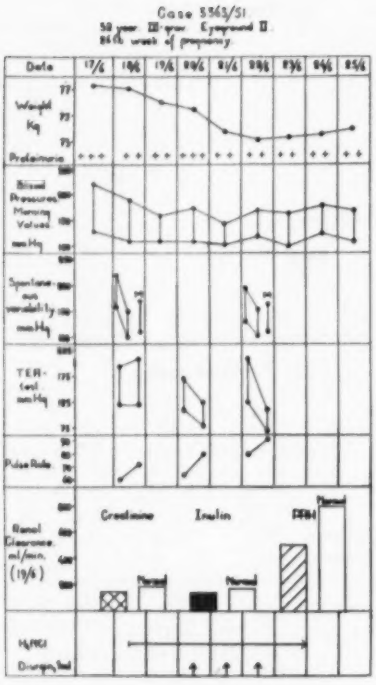

FIG. 3

Proteinuria, body weight and blood-pressure studies during weight-loss due to dehydration in a case of toxaemia of pregnancy. (Diurgin=mercurial diuretic.) Note the increased response to TEA after loss of fluid, although the mean diurnal blood-pressure, the proteinuria and the general condition of the patient were unchanged.

bradycardia. This is in conformity with the results of Jarisch and Richter (1939) and von Bezold and Hirt (1867). Amann and Schaefer (1943) showed that the electrical activity in the vagal fibres was markedly enhanced after veratrum alkaloids.

Several workers have found marked blood-pressure drop in hypertensive cardiovascular disease both after intramuscular administration of veratrone and after long-term treatment with the drug given by mouth. Also in toxaemia of pregnancy its hypotensive effect has been noted, but the only exact study made is the one by Assali, Kistner and Garber (1949), who found a marked and well-controlled decrease of the blood-pressure after veratrum parenterally. Our results confirm this, using the intramuscular route. The individual reaction, however, is rather varied and for treatment small doses must be given, repeated if necessary. The hypotensive effect lasts for a considerable time and may be used therapeutically as shown by several authors.

Of more theoretical interest are the results with tetra-ethyl-ammonium bromide (TEA). TEA acts by blocking the autonomic ganglia and exerts its effect 1–10 minutes after the intravenous administration. In hypertensive cardiovascular disease an immediate blood-pressure fall, usually accompanied by increased pulse-rate, is seen. The cardiac output usually does not change.

In several studies Assali, Brust and co-workers (1949–1952) have demonstrated a marked blood-pressure drop in normal pregnant women at term after TEA or a high selective spinal block. From these results they have concluded that the blood-pressure is maintained during pregnancy by higher neurogenic tone than in the non-pregnant individual. There are several facts pointed out by these authors that indicate that the blood-pressure fall after TEA in the near-term pregnant women is due to pooling of blood in the legs, decreased venous return to the heart, and decreased cardiac output. The assumption that the blood-pressure is not controlled by the same mechanism as in the non-pregnant has thus been concluded from the inability to maintain the blood-pressure in the face of decreased cardiac output. However, Burt (1950) has demonstrated that the sympathetic vascular tone in the extremities is rather decreased at the end of pregnancy, with higher skin temperature and higher skin and muscular blood-flow. In some pregnant women, furthermore, the decrease of venous return that results in the recumbent position due to pressure of the uterus on the large abdominal veins is in itself enough to cause a decrease of blood-pressure or even collapse. These observations thus rather indicate decreased sympathetic tone during pregnancy and not increased neurogenic control of the circulation. Freis and co-workers (1951) showed that during the influence of TEA and other hypotensive drugs (except veratrum) collapse, or at least marked lowering of the

blood-pressure, was easily produced by congestion in the legs in normal individuals. This observation suggests that the pressure of the enlarged uterus may cause enough pooling of blood in the legs to cause a similar collapse. The same workers also produced evidence to show that the inability to increase vasoconstriction in other regions of the body under the influence of sympatholytic drugs was of importance, and not the magnitude of blood-pooling. The evidence for increased neurogenic control during normal pregnancy is thus not conclusive.

Assali and co-workers also found no or a smaller pressure fall after TEA in toxaemic pregnancy as compared with normal. This was interpreted as showing that the blood-pressure was maintained by a humoral factor in toxaemia. In the present series, however, the TEA exerted a marked blood-pressure-lowering effect in all cases of toxaemia. Our mean TEA floor for diastolic blood-pressure was 76.5 mm.Hg, while Brust *et al.* (1948) in no case had a diastolic floor below 80 mm.Hg. In 3 of our 20 cases the TEA floor was 25, 35 and 55 mm.Hg respectively, thus even lower than the diastolic TEA floor for normal term pregnancy (56 mm.Hg) in the material of Brust *et al.* (1948). This difference could be due to different clinical material. Our series of cases is, however, chosen with the same criteria as the American series. Both contain a certain number of previous hypertensive patients, but all cases at the time of study had signs of superimposed toxaemia, in several cases severe with premature delivery and death of the foetus. Different dosage could likewise not account for the different result, as we usually gave a slightly lower dose (5 mg./kg. body weight) than Brust *et al.* (1948) (400 mg.). The only real difference in the technique is that our patients had been on a salt-poor diet, usually with 4–6 g. ammonium chloride added, for 2 or more days at the time of the test, while Brust's patients had no treatment whatsoever. In some cases the effect of this treatment was studied (see Fig. 4). In this case the reduction of the weight with removal of some extracellular fluid (only slight oedema) and increased sodium excretion also increased the reaction to TEA markedly. The state of toxaemia, however, was not improved, with the same mean daily blood-pressure, increasing subjective symptoms and premature spontaneous delivery. Ferris, Reiser, Stead and Brust (1948) have shown that in hypertensive cardiovascular disease some patients react to measures to increase the sodium excretion with decreasing TEA floor. The result of the present series indicates that the same is the case with patients with toxaemia of pregnancy. In this case the high TEA floor found by Brust *et al.* (1948) is not due to a humoral factor regulating the blood-pressure, but to increased sodium and water retention. The increased extracellular fluid may decrease the possibility of pooling in the legs by purely mechanical means. As soon as this fluid retention is reversed the high blood-pressure in toxaemia reacts to sympathetic blocking agents. Assali and co-workers have also seen some cases where increased response to TEA has been interpreted as improvement of the toxaemia. In our cases, where repeated studies were done, the response to TEA increased parallel to the decrease in weight and increased sodium excretion. The toxaemic state was otherwise not influenced; we have not seen any case of toxaemia of pregnancy cured before delivery. The difference between our results and those of Brust, Assali and co-workers (1948) is thus probably due to different degrees of oedema and sodium retention in the two series.

These results illustrate the difficulties in comparing results obtained in studies of toxaemia of pregnancy in different parts of the world. Toxaemia of pregnancy is a dynamic disease, usually either progressing or regressing. It is of the utmost importance to define clearly during which phase each result is obtained, as the findings may be completely different in the same patient from day to day. Another factor of importance in all studies of normal or pathological pregnancy is the stage of pregnancy at which the study is carried out, as the normal physiology of pregnancy undergoes marked changes during the last months. Normal values change markedly from the 8th to the 10th lunar month. There was, however, no correlation between the length of pregnancy and the reaction to TEA in the present series.

Of the drugs tested only veratrone seems to have the therapeutic possibilities. The main difficulty with this preparation is to standardize

the dosage. The development of purer veratrum extracts (veriloid or protoveratrine), which may also be given intravenously, indicates the possibility of more specific and exact treatment of the blood-pressure increase in toxaemia of pregnancy.

Summary and Conclusions

(1) The effect of sodium amytal, sodium nitrite, dehydroergocornine, veratrone, and tetraethyl-ammoniumbromide on the blood-pressure in cases of toxaemia of pregnancy was studied in acute experiments and compared with the spontaneous variability of the blood-pressure in a 24-hour reading.

(2) Sodium amytal, sodium nitrite and dehydroergocornine all gave a small blood-pressure drop of comparable magnitude. The lowest blood-pressure during the influence of these drugs was not statistically different from the lowest spontaneous pressure found.

(3) After TEA and veratrone a more marked blood-pressure fall was induced. This blood-pressure fall was the same for both drugs. The lowest blood-pressure during the action of these drugs was significantly lower than the lowest spontaneous pressure.

(4) In some cases repeated TEA tests showed increased reaction to TEA when the body weight decreased and the sodium excretion increased due to the administration of ammonium chloride and mercurial diuretics. This was interpreted as indicating that a high TEA floor in toxaemia is due to increased sodium retention and cannot be used to show that the blood-pressure is maintained by a humoral mechanism.

(5) The therapeutic possibilities of veratrum alkaloids are pointed out.

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THE EXCHANGE OF SODIUM BETWEEN PLASMA AND EXTRACELLULAR COMPARTMENTS IN PREGNANT WOMEN AS DETERMINED BY Na^{24} TRACER METHODS

BY

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THE exchange of sodium between the various fluid compartments of the human body has been determined by a number of workers (Burch, Reaser, and Cronvich, 1947; Kaltreider, Meneely, Allan, and Bale, 1941; Perley, Forbes, and Pennoyer, 1951; Fauvert and Loverdo, 1950). In pregnant women, the disappearance of Na^{24} from the plasma after its intravenous injection was measured in a few cases by Flexner *et al.* (1948).

This paper records the details of tracer studies in 23 pregnant women, the measurement of exchange in the mother being necessary prior to the measurement of the transfer of sodium to the foetus. Most of the studies were made at the time of delivery, which in 9 cases was spontaneous. In another 9 cases delivery was by Caesarean section without labour. Two cases at term were studied before the onset of labour, and 3 cases of early pregnancy were studied at the time of performing abdominal hysterotomy.

METHOD

An intravenous injection of 10 ml. isotonic sodium chloride solution labelled with approximately 50 microcuries of Na^{24} (half-life 14.9 hours) at the time of injection was given into the antecubital vein of the mother. The syringe was then discarded. The needle was washed through with sterile saline, and was connected by a 3-way tap with a drip infusion apparatus containing normal saline. A slow infusion was maintained to keep the needle and vein patent. Between 50 and 100 ml. of infusion fluid were given in the course of each experiment.

At intervals varying from 1 to 5 minutes, blood samples were withdrawn and collected in heparinized tubes. These samples were centrifuged and the plasma, measured with a micropipette, diluted to a total volume of 10 ml. for each specimen. The radio-activity was estimated using an M6 liquid G.M. counter (Veall, 1948), the chamber of which held exactly 10 ml. of liquid. The counting rates obtained were of the order of 100–2000 counts per minute (for 1–2 ml. of plasma diluted to 10 ml.). Three to 5 counts for each specimen were made and the average taken. (Background counts were of the order 10–20 per minute.) The mean of 5 counts of 100 per minute gives an accuracy of ± 5 per cent; 3 counts of 2,000 per minute of ± 1 per cent. Corrections for background and for radio-active decay were made, and the results plotted as counts/ml. plasma with respect to time. The counter was calibrated at intervals using potassium carbonate (Chalmers, 1951).

The radiation dose received by a patient of 70 kg., when 50 microcuries of Na^{24} is injected intravenously, is less than 0.1 r per day. If the foetus remains *in situ*, and equilibrium occurs between Na^{24} levels in maternal and foetal extracellular spaces, the foetus receives the equivalent of 0.05 r per day. These are below the permissible daily tolerance dose (Marinelli, Quimby, and Hine, 1948).

When 50 microcuries of Na^{24} are used to label 10 ml. of isotonic NaCl solution, the resulting

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dilution of Na^{24} atoms in Na^{23} atoms is 1 in 6,500 million.

In the cases which were not delivered shortly after the injection of Na^{24} the volume of urine excreted was measured, and the radio-activity of samples was assayed using the M6 liquid counter. During the first 2 hours of the experiments the greatest amount of Na^{24} excreted was 0.275 per cent of the quantity injected. There is, therefore, to an accuracy of 1 per cent, no correction to be made for Na^{24} lost through urinary excretion.

It is likely that some Na^{24} is excreted in the sweat, but any loss in this respect was not estimated. However, bearing this possibility in mind, all patients were kept under constant atmospheric conditions throughout the experiments, namely, in the delivery room or operating theatre maintained at 65–70°F. with a high humidity. The main part of the experiment never lasted more than 1 hour, and it is hoped that sweat loss during this time did not introduce an appreciable error in the results.

Results

The values obtained from each case were plotted as counts/min./ml. plasma against time, and a smooth curve was drawn between the points. This curve fell steeply at first, then approached an equilibrium value after 30–45 minutes. In a few cases the experiment was continued for many hours, and a slight diminution continued throughout the whole period of observation. For the purposes of comparison cases were normalized to an equilibrium value of 1,000 counts/min./ml. plasma (Fig. 1). This method of standardization avoids the assumption of any particular value for the plasma volume. The observed equilibrium value was used to calculate the " sodium space " of the mother.

The normalized values were then plotted on semi-logarithmic paper (Fig. 3) and it was found that each curve can be analyzed into two exponential components, the first component having a half-life of 60–70 seconds, and the second a half-life ranging from 6 to 10 minutes.

The equation relating the coefficients of these two components is:

$$(1) \qquad Cp - C_\infty = \alpha_1 e^{-\beta_1 t} + \alpha_2 e^{-\beta_2 t}$$

(Gellhorn, Merrell, and Rankin, 1944).

The coefficients were determined in each case. Although the values obtained ranged about mean for the whole series, it was found that the cases can be divided into 2 groups according to variations in the values for α_2 and β_2.

The first group comprised: 2 cases of normal pregnancy at term, not in labour; 2 cases of early pregnancy at the time of performing hysterotomy.

The second group comprised: 18 cases of normal pregnancy at term at the time of delivery; 1 case of early pregnancy at the time of performing hysterotomy.

The coefficients are displayed in Table I.

Using these measured coefficients of Groups 1

Table I

$$Cp - C_\infty = \alpha_1 e^{-\beta_1 t} + \alpha_2 e^{-\beta_2 t}$$

Group	Cases	C_∞	α_1	β_1	α_2	β_2
1	2 normal pregnancy not in labour 2 early pregnancy (hysterotomy)	0.147	0.69	0.57	0.172	0.0945
2	18 normal pregnancy at delivery 1 early pregnancy (hysterotomy)	0.215	0.646	0.57	0.138	0.076
3	3 normal pregnancy not in labour	0.306	0.404	0.521	0.289	0.0702
4	17 normal cases human	0.20	0.67	0.46	0.13	0.046
5	1 normal case human	0.29	0.53	0.58	0.18	0.064

Groups 1, 2: Our experiments.
Group 3: Values obtained from published graph of Flexner *et al.* (1948).
Group 4: Values from published data (Fauvert and Loverdo, 1950).
Group 5: Values from published data (Burch *et al.*, 1947).

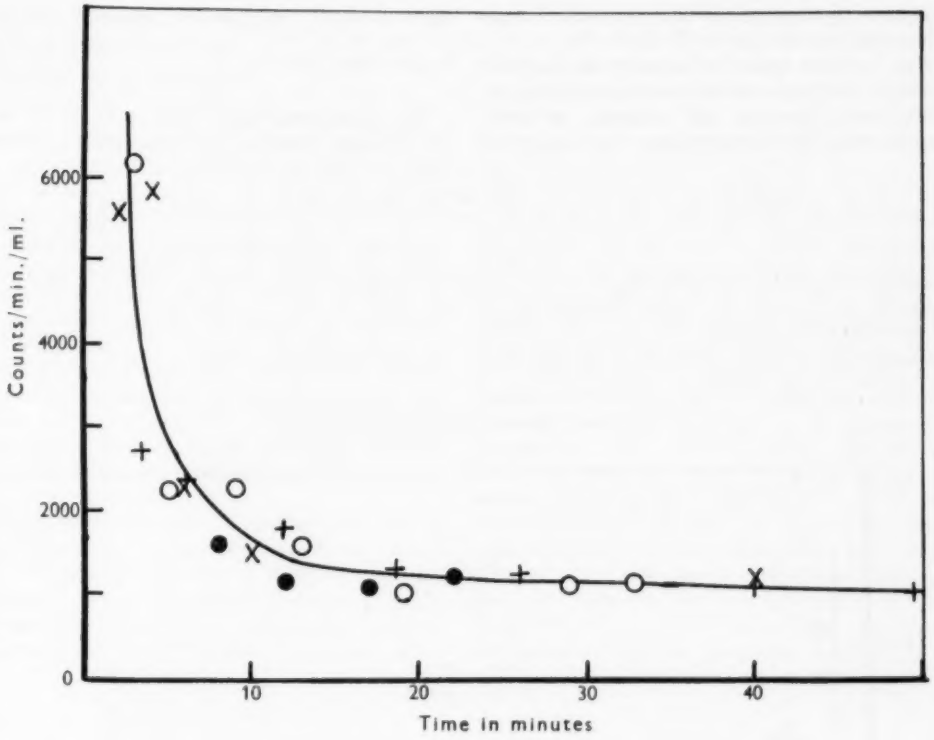

FIG. 1
Plasma concentration curve of Na^{24} for pregnant women. Group 1. Four cases.

× = Not in labour.
O = Early pregnancy (hysterotomy).
+ = Not in labour.
● = Early pregnancy (hysterotomy).

and 2 an expression can be derived for the quantities of sodium diffusing per minute from the plasma to the interstitial fluid, and in the reverse direction.

The percentage of total sodium in the interstitial fluid

$$(2) \qquad = \frac{\alpha_1 + \alpha_2}{C_o} \times \frac{100}{1}$$

(Burch, Reaser, and Cronvich, 1947)

C_o is the extrapolated initial count per minute per millilitre of plasma.

$$C_o = C_\infty + \alpha_1 + \alpha_2.$$

The percentage of plasma sodium diffusing out of the vascular bed per minute

$$(3) \qquad = \frac{\alpha_1\beta_1 + \alpha_2\beta_2}{C_o} \times \frac{100}{1}$$

(Burch, Reaser, and Cronvich, 1947)

The percentage of the total interstitial fluid sodium diffusing into the vascular bed per minute

$$(4) \qquad = \frac{\beta_1 (1 - q)}{q} \times \frac{100}{1}$$

$$q = \frac{\alpha_1 + \alpha_2}{C_o}$$

(Merrell, Gellhorn, and Flexner, 1944).

The absolute values of the quantities involved in equations (3) and (4) are the same.

The average values for Groups 1 and 2 were calculated, and are shown in Table II.

The " sodium space " (Kaltreider *et al.*, 1941) is calculated from the plasma radio-activity at equilibrium, knowing the quantity of Na^{24} injected into the blood-stream. An aliquot of the radio-active injection is taken and assayed.

$$\text{Sodium space (ml.)} = \frac{\text{Total counts/min. injected}}{\text{Counts/min./ml./plasma}}$$

The values are summarized in Table III and are plotted showing sodium space against

TABLE II

	Group 1	Group 2	Non-pregnant women*
Percentage of sodium in interstitial fluid	85.2	78.4	70
Percentage of total plasma sodium diffusing out of vascular bed per minute	40.2	38.0	32
Percentage of total interstitial fluid diffusing into vascular bed per minute	6.9	10.5	13

* Burch, Reaser and Cronvich (1947)

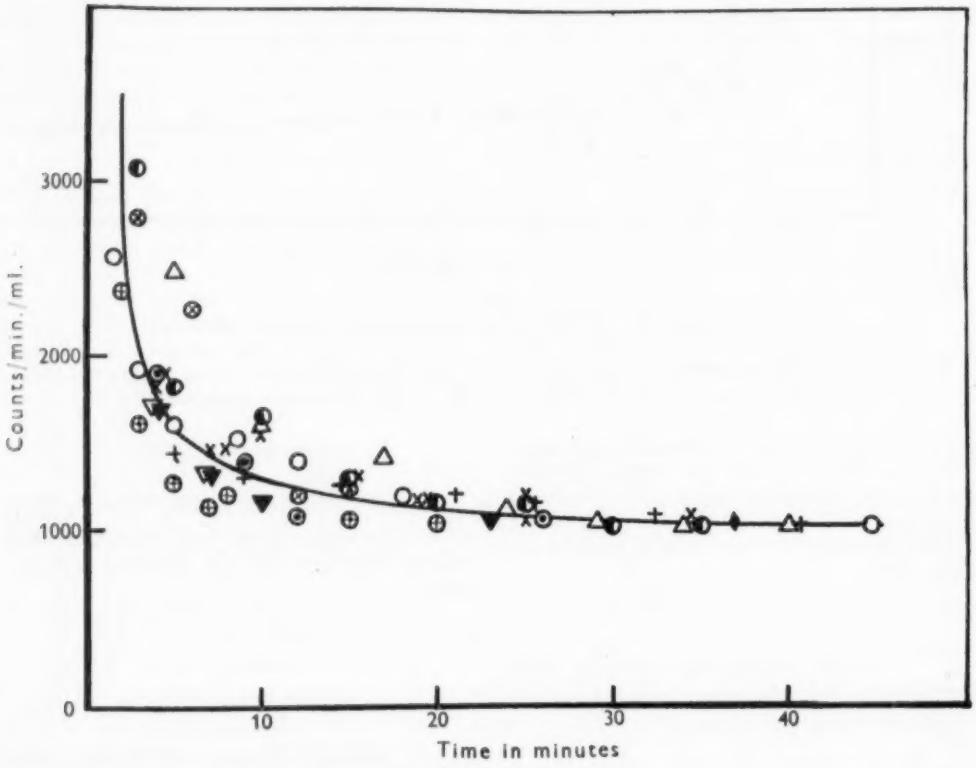

FIG. 2

Plasma concentration curve of Na^{24} for pregnant women. Group 2. Nineteen cases, including one of early pregnancy.

weight of pregnant woman (Fig. 4). The average value at term (18 cases) is 27.9 ± 5.6 per cent of body weight.

Discussion

From the aspect of sodium exchange studies, the pregnant woman differs from the non-pregnant woman in having an increased plasma volume (Roscoe and Donaldson, 1946; Tysoe, Lowenstein, and Simon, 1950) and in having an additional compartment, the foetal sac, with which exchange of sodium occurs. The extracellular fluid volume, measured by the thiocyanate method, is also increased during pregnancy (Caton, Roby, Reid, and Gibson, 1949). The values found for the sodium space in this series (27.9 ± 5.6 per cent body weight) are a little higher than the values found by Perley *et al.* (1951) in healthy adult males (25.3 ± 4.02 per cent body weight).

The rate of exchange of sodium between the plasma and the extracellular space up to the time of equilibrium can be inferred from the maternal plasma concentration curve of Na^{24}. Immediately after injection all the tracer sodium is contained in the maternal plasma. Other workers (Fauvert and Loverdo, 1950) observed a series of waves (3 in the first minute) by recording the gamma radiation over an artery following intravenous injection of Na^{24}. These waves are no doubt due to recirculations. We did not take specimens at this short time interval.

The next stage is one of diffusion of Na^{24} out of the plasma. The plasma concentration curves determined by us show a double exponential form over the first hour, by which time most of our experiments were concluded. Other workers (Kaltreider *et al.*, 1941; Manery and Bale, 1941; Burch *et al.*, 1947; Fauvert and Loverdo, 1950, in human beings; and Gellhorn, Merrell, and Rankin, 1944; Morel and Marois, 1949 in animals) found evidence of 3 or 4 exponential components over a longer period. The observations in humans indicate a number of simultaneous processes of transfer of Na^{24} out of the maternal plasma, at different rates. It has been suggested (Manery and Bale, 1941) that these different rates are due to the transfer taking place to different fluid compartments of the body. Fauvert and Loverdo (1950), summarizing previous reports, postulate that the first

Table III

Case	Method of delivery	Age	Weight before delivery (kg.)	Sodium space per cent body weight
1	C.S.	26	57.5	27.2
2	C.S.	33	72.2	27.8
4	C.S.	41	55.5	24.9
5	C.S.	28	62.5	19.7
6	C.S.	28	63.0	21.5
7	C.S.	34	51.5	26.1
8	Undelivered	29	61.5	27.1
9	Normal	21	64.0	32.1
13	Forceps	30	68.0	33.1
14	Normal	30	65.0	34.8
15	Undelivered	31	86.0	25.4
17	Normal	39	70.0	23.8
21	Normal (twins)	40	71.0	29.8
22	Normal	25	53.0	28.0
28	C.S.	26	53.0	43.7
32	Normal	29	53.5	30.1
39	Hysterotomy	38	48.0	23.1
40	C.S.	31	75.0	24.6
43	C.S.	25	63.5	22.6

C.S. denotes Caesarean section.

exponential component, or "rapid" phase of diffusion is due to transfer of Na^{24} to a volume of the interstitial fluid about 3 to 4 times the plasma volume, and that the second component, a "slow" phase of diffusion, is due to transfer of Na^{24} to a volume of interstitial fluid which is about 6 times the plasma volume. The third component, which we have observed only in 3 long duration studies, is due to transfer of Na^{24} to a volume of fluid which is about 7 times the plasma volume.

The previous workers suggested that exchanges take place as if there were a series of compartments. If V = plasma volume, and A + B + C = total interstitial fluid volume, then the "fast" diffusion is from V to A. The "slow" diffusion is from V or from (V + A) to B, and the final very slow diffusion from V or (V + A + B) to C. At equilibrium the measurement of the concentration in V + A + B + C gives a value for the "sodium space". In animals, the "fast" diffusion is into the following tissues:

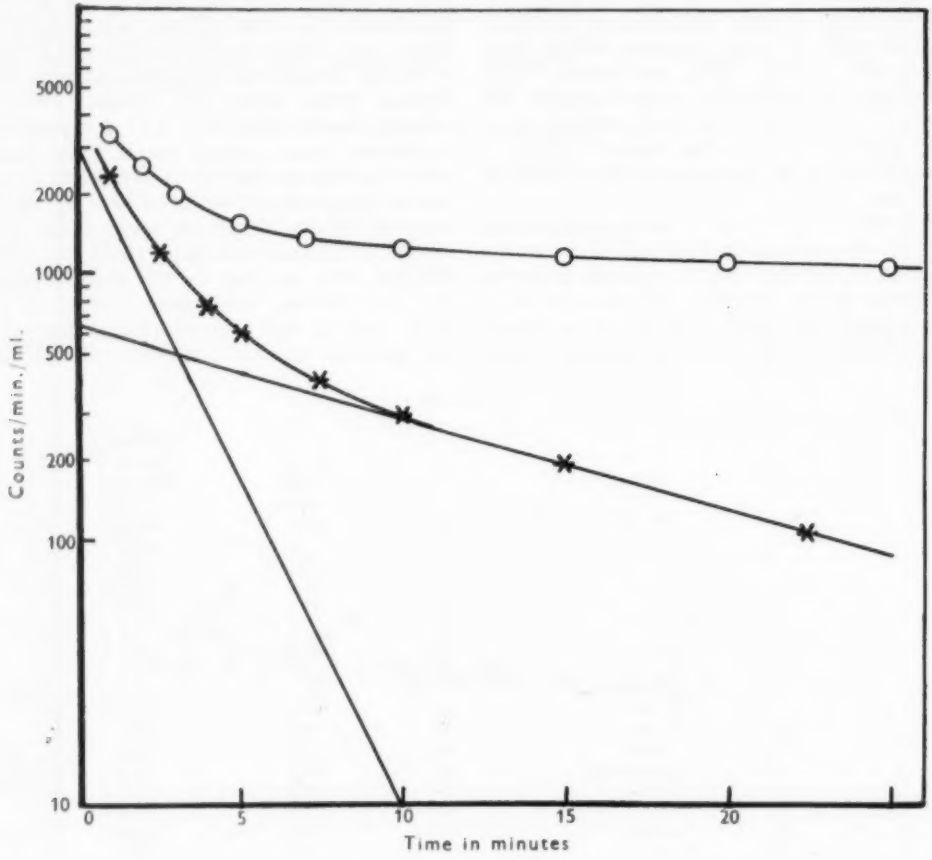

FIG. 3

Plasma concentration curve of Na^{24} for pregnant women. Semi-logarithmic plot showing the exponential components.

$$Cp - 1000 = 3000\ e^{-0.57\ t} + 650\ e^{-0.76\ t}$$

muscle, liver, intestine, and kidney; and the "slow" diffusion is into brain, nerves and bones (Manery and Bale, 1941; Gellhorn *et al.*, 1944).

The "fast" rate of diffusion out of the plasma (β_1) which we have measured appears to be within the normal range of values previously reported, although the plasma volume is increased during pregnancy. The "slow" rate of diffusion (β_2) we find to be slightly increased during pregnancy. This is in accordance with the increased extracellular space for pregnant women.

So far we have assumed that Na^{24} exchanges only with the sodium in the extracellular spaces. It is probable that this is incorrect and that Na^{24} does exchange slowly with the intracellular sodium. For example, the red blood cell membrane is permeable to Na^{24}, and allows sodium to pass in either direction at a very slow rate provided that the internal concentration of sodium and potassium remains unchanged (Cohn and Cohn, 1939; Moore, 1946). When the values published in their paper are plotted graphically there appears to be evidence of an exponential rate of transfer. If a similar relationship exists between intra- and extracellular sodium for all body cells, then a slow component of the diffusion rates which extends over many hours may be due to the transfer of Na^{24} to the intracellular spaces.

There is another possible explanation for a slow component of the diffusion rates over several hours. Evans, Lenz, Donlan, and Le May (1948), investigating the effect of therapeutic doses of 17 millicuries of Na^{24} on leukaemia, were able to measure the Na^{24} con-

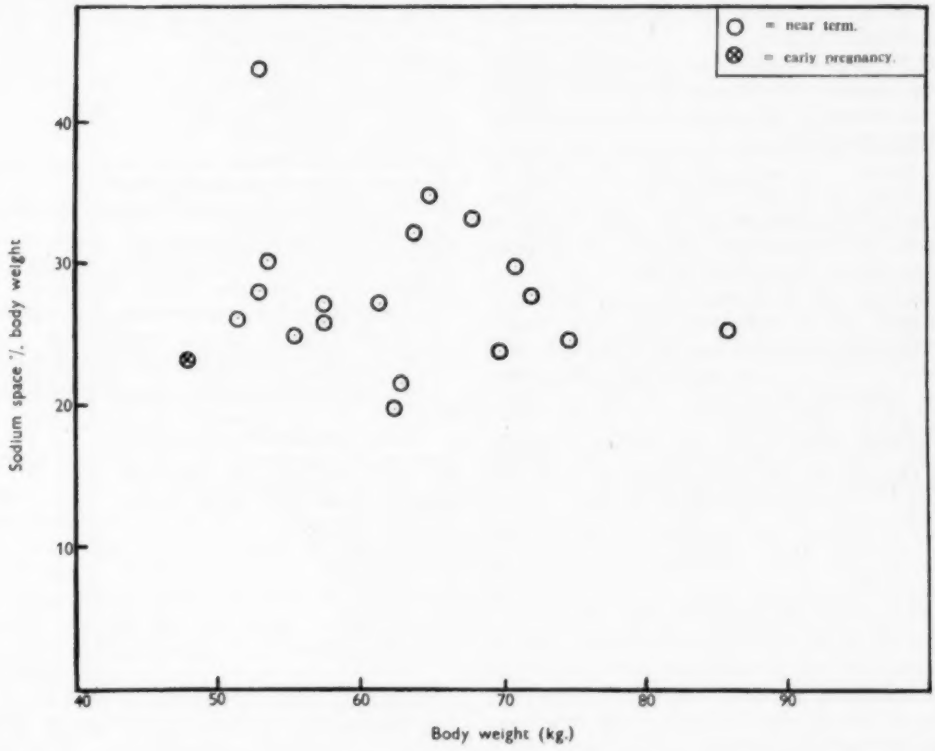

FIG. 4

Sodium space in normal pregnancy, 19 cases.

tent of bones in 2 children who died 2 days after a large injection of Na^{24}. They found that the activity per gram net weight of the vertebrae was 1.84 and 2.75 times respectively that of the average of the body. *In vitro* experiments by Hodge *et al.* (1943) showed that bone, dentine, and enamel take up Na^{24} from a solution of radio-active NaCl, and these authors suggest that the adsorbing power of bone is great enough to explain the quantity of sodium present *in vivo*. It appears that a possible explanation of a slow diffusion rate from the plasma is due to the adsorption by bone of Na^{24}.

The actual quantities involved in these transfers are quite appreciable. Assuming a plasma volume of 57.1 ml. kg. in pregnancy (Tysoe *et al.*, 1950), the sodium contained in the plasma in a woman of average weight (our series 62.6 kg.) is 12.1 g. (3.3 mg. sodium/ml. plasma, Peters and Van Slyke, 1931).

If 40 per cent of this sodium leaves the plasma every minute, this means a transfer of 4.8 g./minute or 288 g./hour from plasma to extracellular compartments.

Summary

(1) Isotonic NaCl labelled with Na^{24} was injected intravenously in 23 cases during pregnancy and at the time of delivery.

(2) The rate of disappearance of Na^{24} from maternal plasma was measured. The plasma concentration curves plotted against time showed evidence of at least two exponential components. The constants determined indicate a "fast" rate and a "slow" rate.

(3) The sodium space at partial equilibration has been determined, the average value at term being 27.9 ± 5.6 per cent body weight.

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THE TRANSFER OF SODIUM ACROSS THE HUMAN PLACENTA DETERMINED BY Na^{24} TRACER METHODS

BY

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THE introduction of radio-active isotopes offers new methods for the study of placental function, particularly of the transmission of radio-actively labelled physiological substances from mother to foetus and vice versa. Pohl and Flexner (1941) were the first to explore this field of investigation. They injected isotonic sodium chloride tagged with Na^{24} into the maternal blood-stream, and measured the quantity of Na^{24} transferred to the foetus. The comparative results in animals were summarized by Flexner and Gellhorn (1942) and Gellhorn, Flexner and Hellman (1943) published a preliminary report on transfer in the human. In animals they were able to reach more definite conclusions because the animals and newborn were killed and analyzed at the end of each experiment, and the foetal content of radio-activity assayed. Similar complete experiments can be carried out in the human being only when there is reason for the planned delivery of a non-viable foetus.

MATERIAL AND METHODS

This communication is concerned with the study of 20 cases, in 3 of which the foetus was non-viable, and available for complete analysis. Of the remaining 17, 6 were delivered spontaneously (1 set twins), 2 were delivered with forceps, and 9 were delivered by Caesarean section without previous labour. These latter operations were mainly repeat sections for contracted pelvis.

1. *In cases of non-viable pregnancy*, preparations having been made for abdominal hysterotomy, an intravenous injection of 10 ml. isotonic sodium chloride solution containing approximately 50 microcuries Na^{24} at the time of injection was given according to the method already described (Cox and Chalmers, 1953).

At intervals varying from 1 to 5 minutes samples of maternal blood were withdrawn and were collected in heparinized tubes. These samples were collected until several minutes after delivery of the foetus and placenta.

Following the initial injection, anaesthesia was induced, in 2 cases with curare, thiopentone and cyclopropane; but in one case local infiltration analgesia alone was used. Abdominal hysterotomy was performed, the uterus being opened by a mid-line incision in the anterior wall. The gestation sac containing the liquor amnii was removed entire in 2 cases, and in the third the placenta was removed undamaged although the liquor was spilt.

Specimens of the liquor and cord blood were obtained, and the quantity of liquor measured. The foetus and placenta were weighed separately, then each was finely minced and separated into 3 portions, each of which was weighed. The weight of placenta was measured after separating the umbilical cord, amnion, and chorion. This was done to express the results in terms of grams of placental tissue which is capable of transporting sodium. The discarded membranes, from the point of view of placental transmission, may be considered avascular. The secundines may weigh as much as 20 per cent of the placenta. One portion of foetus and one of placenta were treated in each of the three following ways:

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(1) Mixed with a known volume of water, heated gently, then centrifuged and the supernatant fluid taken for examination.
(2) Wet ash incineration performed, the material being dissolved in sulphuric acid and nitric acid.
(3) Dry ash incineration performed, the residue being dissolved in hydrochloric acid.

The specimens of maternal and foetal blood were centrifuged, and the plasma, measured with a micro-pipette, was assayed for radio-activity as already described in the previous paper.

The specimens were examined after the Na^{24} had decayed to less than 1 per cent to determine whether any of the observed radio-activity was due to K^{40}, the isotope present in one part in 9,000 in all potassium. Negligible residual activity was found.

Chemical analysis of the foetus and placenta was made in one case by the uranyl method.

2. *In cases delivered at term* the procedure was exactly the same as detailed for the cases of hysterotomy, up to the point of incising the uterus in cases of abdominal delivery. The lower uterine segment was incised, and then, on rupturing the membranes, an aspirator was inserted into the amniotic cavity to withdraw the liquor. The volume of liquor was measured and a specimen retained for examination. In cases where the liquor was heavily contaminated by maternal blood from the uterine wound, the volume only was measured.

The child was then delivered and the cord immediately clamped in three places. One clamp was placed about 6 inches from the umbilicus, and another within an inch of the first. The cord was divided between these clamps. The third clamp was placed as near the vulva or, in cases of Caesarean section, as near the uterine wound as possible. The third clamp isolated a volume of about 10–20 ml. of foetal blood in the cord. This specimen was later collected in a heparinized tube and saved for examination. During the extraction of the child an injection of 0.5 mg. ergometrine was given intravenously to the mother, with the result that a sustained contraction of the uterus occurred, expelling the placenta usually 1 or 2 minutes after the child. The placenta was collected in a sterile dry receiver and the cord blood isolated between the clamps was collected. A needle was then inserted into one of the large veins on the foetal surface of the placenta, and 10–20 ml. of blood withdrawn with a syringe and collected in a heparinized tube. The cord was then divided at its origin on the placenta and the organ squeezed manually in an attempt to expel the foetal blood. The volume of this expressed blood did not exceed 30 ml. in any case. The membranes of the placenta were removed and the organ weighed. A section of placenta was taken for histological examination.

In a few cases a specimen of infant blood was withdrawn from the fontanelle or from the external jugular vein 1 hour after delivery. Blood was not collected from premature infants, and because of the slight risk even to an infant at term, this procedure was not made a routine.

In those cases where normal vaginal delivery took place, the technique varied only in that, as the membranes were already ruptured, no collection of amniotic fluid was made, and the normal separation of the placenta was allowed without the exhibition of ergometrine. In cases where general anaesthesia was administered for forceps delivery, ergometrine was given as usual, and the placenta was expelled in 1 or 2 minutes.

Radio-active assay was performed as already described.

Results

1. *In cases of non-viable pregnancy.* When a non-viable foetus is available for complete analysis, the quantity of sodium transferred from the maternal plasma to the foetal tissues in the time (t minutes) from injection to delivery is:

$$\frac{\text{Total counts/min. of foetus + liquor + placenta} \times 3.3}{\text{Counts/min./ml. maternal plasma}} \text{ m.g.}$$

This is derived from the expression

$$\frac{Na^* mp}{Na\ mp} = \frac{Na^* f}{Na\ f}$$ (Flexner, Cowie, *et al.* 1948).

The average value for Na^* mp to the time t is obtained by plotting the plasma concentration curve.

Na mp is assumed to be 3.3 mg./ml. (Peters and Van Slyke, 1931).

By making use of various published values for the quantity of sodium found in the foetus at varying gestation periods, a graph was plotted of sodium content against body weight (Fig. 1). This graph was used to find the expected sodium content in the foetuses which were not chemically analyzed. From the data of Streeter (1920) a graph was plotted to show the expected daily increase in weight for a foetus of given size (Fig. 2). The quantity of sodium retained per day was thus calculated. Sodium is supplied in excess of this value, and Pohl and Flexner (1941) have termed the ratio $\frac{\text{Sodium supplied/day}}{\text{Sodium retained/day}}$ the " safety factor ".

The " sodium space " is the volume of body water into which sodium freely diffuses. It is almost equivalent to the volume of the extracellular fluid plus the plasma volume. Taking no account of intracellular sodium in the foetus, the expected or theoretical sodium space is:

$$\frac{\text{Foetal sodium (per cent of body weight)}}{3.3} \times 100,$$

3.3 being the sodium content/ml. of foetal plasma (Bruch and McCune, 1936).

If a known quantity of Na^{24} is injected into the body, when equilibrium between the plasma and the extracellular space has been reached, the dilution of the Na^{24} in the plasma gives a measure of the sodium space. In a non-viable foetus the radio-activity of foetal plasma and of the whole foetus can be measured. If equilibrium is reached the sodium space is:

$$\frac{\text{Counts/min. foetus}}{\text{Counts/min./ml. foetal plasma}} \text{ ml.}$$

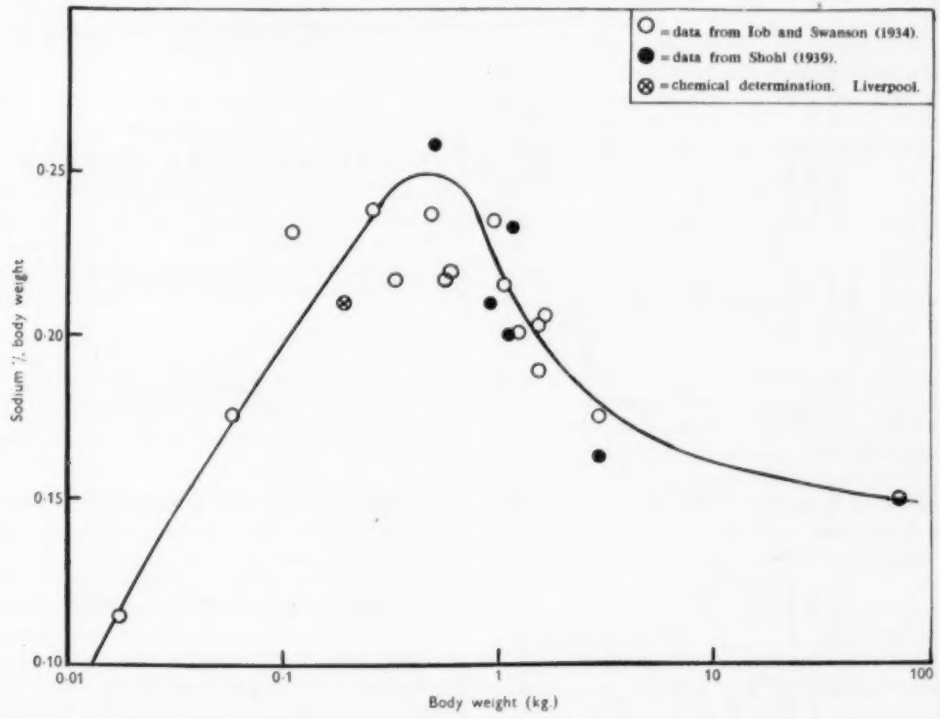

FIG. 1

Graph showing the percentage of sodium in the body for different weights.

TABLE I

Case No.	Indication for hysterotomy	Foetal age (weeks)	Foetal weight (g.)	Placental weight (g.)	Foetal sodium total per cent	Daily weight increase	Sodium retained mg.	Sodium suppld. mg./day	Sodium suppld. mg./g. placenta /hour	Safety factor	Theoretical sodium space of foetus per cent body weight	Observed sodium space of foetus per cent body weight
10	Cancer gall bladder	18	190	60	0.21*	3.7	14.76	3585	2.49	243	63.6	55.6
25	Psychoneurosis	14	52	39	0.17†	6.4	5.657	795	0.85	141	51.5	44.1
39	Heart disease	20	211	99	0.235†	3.6	17.85	5132	2.16	288	71.2	84.3

* Chemical analysis. † From graph (Fig. 1).

TABLE II

Case	Method of delivery	Gravidity	Gestation (weeks)	Infant weight (kg.)	Placenta weight (g.)	Cm (normalized) counts/min. /ml.	Cf (normalized) counts/min. /ml.	Correcting factor for maternal plasma	Time (min.)	Sodium transferred (mg.g. placenta/hr.)	$\frac{dQ}{dt}$	Safety factor
1	C.S.	2	40	3.17	400	1328	599	1.52	11	3.20	6.91	451
2	C.S.	4	40	3.26	500	1304	479	1.56	8.5	2.72	8.91	466
4	C.S.	1	38	3.58	450	1313	597	1.48	12.5	2.97	8.80	404
5	C.S.	1	41	3.12	324	1142	382	1.39	20.5	2.04	6.27	235
6	C.S.	3	40	3.46	370	1063	449	1.35	26	1.96	7.01	234
7	C.S.	3	38	2.24	370	1777	347	1.40	20	2.03	10.7	363
11	Normal	1	39	3.08	453	2145	644	1.57	6	3.28	14.9	543
13	Forceps	1	40	2.90	426	1138	988	1.37	24	3.30	1.71	543
14	Normal	6	42	4.34	538	1699	482	1.54	4	5.03	18.7	702
17	Normal	7	39	2.90	554	1166	725	1.42	17	5.54	6.49	1168
20	Forceps	1	42	3.48	480	1226	585	1.56	9	3.66	8.82	568
21	Normal	11	35	2.02	256	—	—	—		—	—	—
	Twins			2.13	298	1000	553	1.44	45*	1.45	3.37	203
22	Normal	3	38	2.72	430	1478	611	1.57	8	3.22	7.88	552
28	C.S.	1	42	3.18	505	1204	416	1.45	14	1.77	10.6	315
32	Normal	2	41	1.94	228	7400	518	1.48	2	2.44	21.1	319
40	C.S.	5	36	2.86	475	1440	542	1.37	23	1.34	11.5	248
43	C.S.	2	39	3.4	510	1200	272	1.57	7	2.06	12.1	339

* Injection of Na^{24} given after birth of first twin. C.S. = Caesarean section

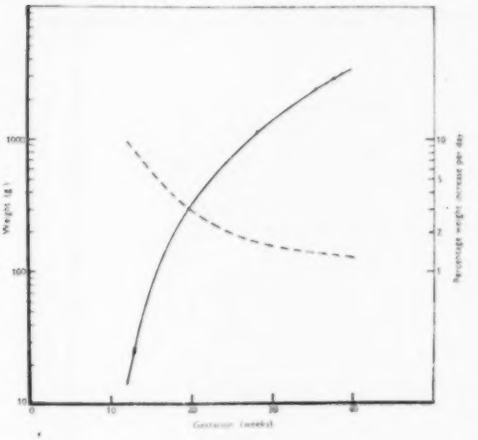

FIG. 2

Graph showing the average growth of the foetus (from Streeter, 1920) and the percentage increase of body weight per day.

——— = growth of foetus.
– – – – = percentage weight increase per day.

The degree of agreement between the "theoretical sodium space" and the observed sodium space shows how nearly equilibrium has been reached between foetal plasma and foetal extracellular fluid.

A simple calculation on Case 10 with a foetus of 190 g. and foetal plasma counts/min./ml. of 122 shows that the extracellular fluid count/min/ml. would have been 106. Equilibrium had nearly been reached in the 14 minutes of the experiment.

In our experiments we observed a high Na^{24} content of the placenta; in 2 of the cases this exceeded the total Na^{24} content of the foetus. We will show that most of this radio-activity was due to sodium actually in passage through the trophoblast or the extracellular tissues of the villi. The placentae were intact after delivery, and were squeezed to expel maternal blood from the intervillous spaces, and foetal blood from the placental vessels. The maternal surface was not washed in case sodium should diffuse out of the placenta. The measurements from Case 10 are as follows:

Placental weight	60 g.
Total counts/min.	10,080
Maternal plasma radio-activity	700 counts/min./ml.
Foetal plasma radio-activity	122 counts/min./ml.

Suppose all the maternal and foetal blood were not squeezed out, and say 6 ml. of maternal and 15 ml. of foetal blood were left in the placenta. The plasma volumes would be half of these. The radio-activity due to these plasmata would be 3,015 counts/min. leaving a balance of 7,065 counts/min. due to the placental tissue. Assuming a 70 per cent water content of the placental tissue, the radio-activity would be 250 counts/min. ml. of intra- and extra-cellular water.

Actually, in the hour that elapsed between collecting the placenta and examining it, some fluid exuded from the surface. This fluid, which probably was extracellular fluid of the placenta, when centrifuged gave 267 counts/min./ml., a figure in good agreement with the suggested figure of 250.

Similar results were obtained from calculations on the other cases.

2. *In cases delivered at term.* We evaluated the sodium transferred to the foetus according to the method of Flexner, Cowie, *et al.* (1948) and obtained results of the same order of magnitude. These results are shown in Table II and Fig. 3. We have inserted the fitted curve of Flexner *et al.*, since we have no values for cases delivered between the 20th and 35th weeks of gestation. The average gestation period of our cases at term was 39 weeks, and the average sodium transfer per gram placenta per hour was 2.8 mg. We examined a number of formulae to determine whether an equation could be found to represent a constant relationship between all normal cases. The equation

$$\int_0^t dQ = K\,A\,(Cm\text{-}Cf)\left(\frac{Pw}{7} + \frac{Fw}{22.2}\right)(Sp)\,dt$$

was evolved and the rate $\frac{dQ}{dt}$ for all normal cases, when plotted against time, showed evidence of an exponential curve (Fig. 6).

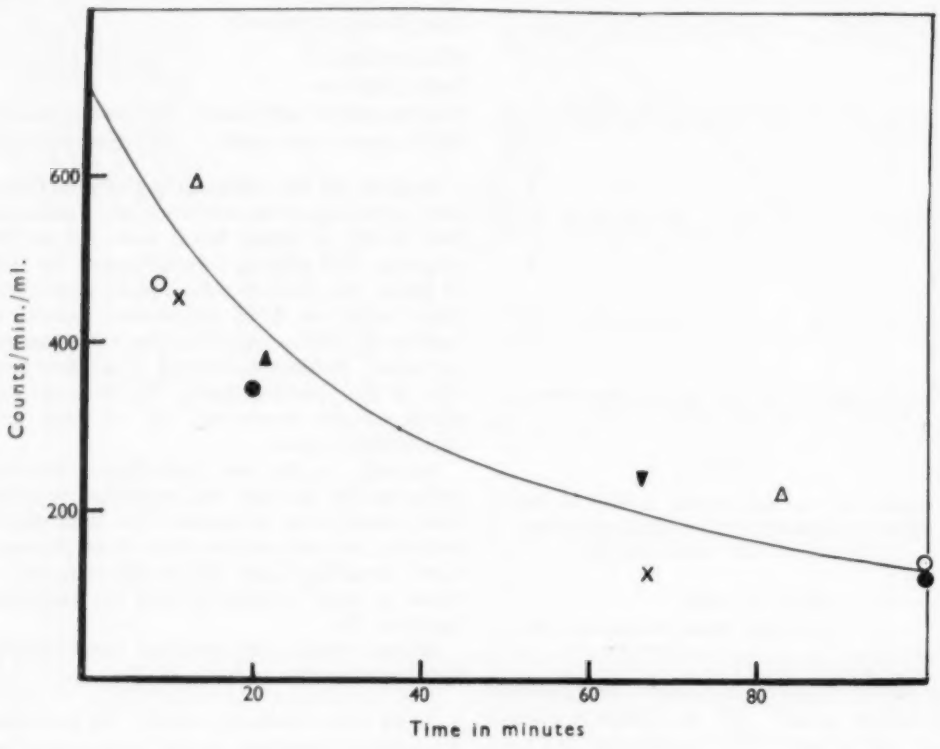

FIG. 3
Graph of infant plasma Na^{24} concentrations. Injection of Na^{24} to mother at $t=0$.
First infant concentration at time of delivery.

$\frac{dQ}{dt}$ = the instantaneous rate of transfer of Na^{24} across the placenta at a time t minutes after injection.
K = the permeability of the placenta.
A = the area of the placenta; in the absence of other information this is presumed proportional to the weight, and this figure is substituted in grams.
Cm = counts/min./ml. ,maternal plasma.
Cf = counts/min./ml. foetal plasma.
Pw = placental weight in grams.
$\frac{Pw}{7}$ = volume of foetal plasma in the placenta (ml.).
Fw = foetal weight in grams.
$\frac{Fw}{22.2}$ = volume of foetal plasma in the foetus (ml.).
Sp = correcting factor for the sodium space of the infant at the time t.

The fact that the values for $\frac{dQ}{dt}$ show some relationship to each other suggests to us that there is some justification for considering this equation further. It is likely that other factors may be found to affect the rate of transfer, and they should be included in the equation. If $\frac{dQ}{dt}$ could be evaluated exactly we believe that a series of values plotted against time, should appear as a single exponential curve.

It is observed that the values for placental transfer of sodium/g. placenta/hour are a little lower in cases delivered by Caesarean section, (2.23 ± 0.60) than in those delivered after labour

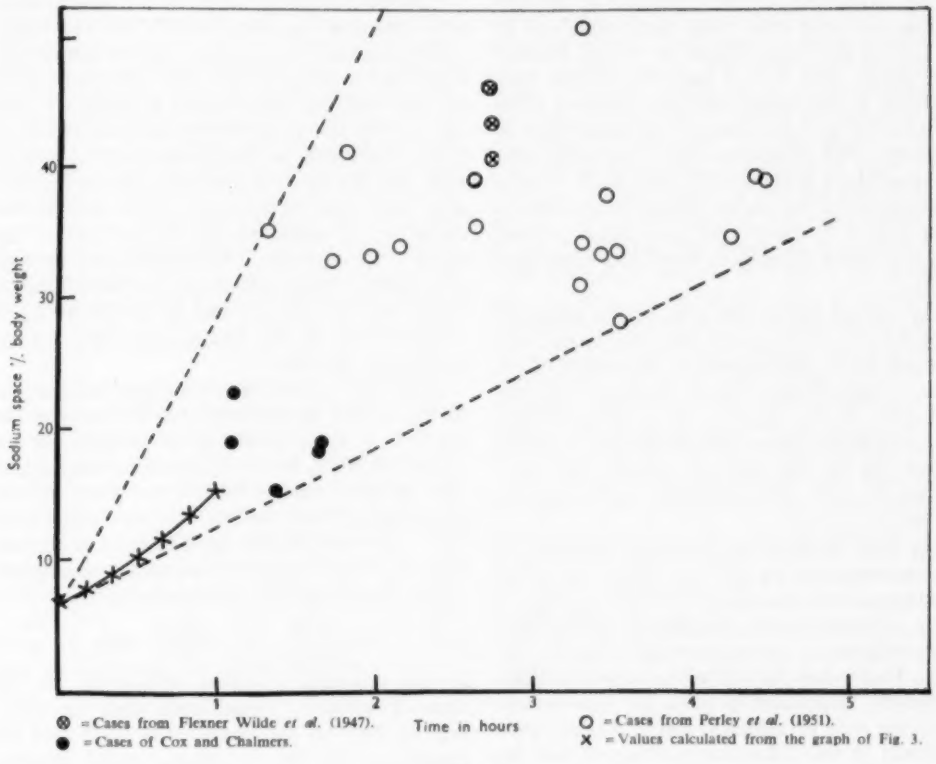

FIG. 4

Graph showing sodium space of infants plotted against time allowed for equilibration.

(3.49 ± 1.31). This is not a significant difference, and suggests that placental function as regards sodium is certainly not diminished by the uterine action of normal labour. No difference is observed in the scatter of values for $\frac{dQ}{dt}$ for these two methods of delivery.

DISCUSSION

Following the moment of injection of Na^{24} into the maternal blood, all the Na^{24} is contained in the plasma. Diffusion out of the plasma to the extracellular space begins immediately. As soon as the circulating Na^{24} reaches the uterine sinuses, transfer across the placenta commences. The Na^{24} is transferred to the foetal plasma, and, while the concentration is building up here, diffusion is already beginning to the foetal extracellular space. Once there is a concentration of Na^{24} in the circulating foetal plasma it is possible that a Na^{24} atom which has just crossed the placenta to the foetus, may cross the placenta in the reverse direction. In an attempt to make any transfer back to the mother as small a quantity as possible, we made our injection-delivery interval a short one. Sometimes, and for many reasons, the expected delivery of the child was delayed. In these cases it is to be expected that the calculated value for sodium transfer may err on the low side.

The formula for $\frac{dQ}{dt}$ was evolved on the theory that the rate of transfer is proportional to the permeability and the area of the trans-

ferring membrane, to the difference in concentrations on either side of the membrane, and to the size of the compartment to which transfer takes place. The first of these factors, the permeability of the membrane, was assumed to be constant for normal cases at the same stage of gestation. The membrane separating foetal and maternal blood is about 0.025 mm. thick in early pregnancy and has three cellular layers, whereas at term it is about 0.002 mm. thick and has only two layers (Hamilton, Boyd and Mossman, 1945).

The second factor, the area of the placental trophoblast in contact with maternal blood, was assumed to be proportional to the weight of the organ. Christoffersen (1934) computed the surface area of the placenta by a serial section method, finding values between 10 and 14 square metres. He did not offer any simple expression relating the area of the placenta to its weight or volume.

The third factor (Cm-Cf), or the difference in the concentrations of Na^{24} on either side of the membrane, is the crucial factor in the expression. When it is introduced, the plotted results show some evidence of an exponential relation with time. Fick's law for diffusion across a semi-permeable membrane is valid for non-electrolytes, the rate of diffusion being directly proportional to the difference in concentration on either side of the membrane. Apart from the fact that sodium is an electrolyte, there is another reason why the transfer of sodium across the placenta may not be proportional to (Cm-Cf). It is possible that sodium is transferred to the foetal circulation, not by diffusion, but by some active process involving work by the placental membrane. Sometimes sodium is transferred from mother to foetus from a weaker to a stronger concentration of sodium. Miller (1941) measured the maternal and infant concentrations of plasma sodium immediately after birth in 29 cases. The infant level was greater in 16 cases, the maternal level greater in 10 cases, and the levels were identical in 3 cases. On the average the infant levels were 2 milliequivalents higher. If the foetal plasma sodium concentrations were always higher than the maternal, a case could be made for the transfer of sodium being by secretion.

Cations cross other membranes from a weaker to a stronger concentration. In the red blood cell, potassium is at a much higher concentration than it is in the plasma. In experiments *in vivo* with the radio-active isotopes P^{32} and Na^{24} Cohn and Cohn (1939) and Moore (1946) found that both isotopes penetrated at a slow rate. We plotted their published figures graphically, and there is evidence of an exponential curve for the uptake of sodium and also for the uptake of potassium. This suggests that the rate of transfer of these ions across the red cell membrane may be proportional to the difference in concentration of the *radio-active* ions outside and inside the cell.

Although we are unable to give evidence as to the nature of placental transfer of sodium, whether it is an exchange mechanism, or an active secretion, or by diffusion, yet we suggest that there is some evidence by virtue of the constancy of our results, that the transfer of Na^{24} is proportional to the difference in concentration of Na^{24} on either side of the membrane.

The final factor in our expression

$$\left(\frac{Fw}{22.2} + \frac{Pw}{7}\right) (Sp)$$

is the "partial" sodium space up to the time of delivery. Immediately after the injection of Na^{24} to the mother, the Na^{24} ions are transferred to the circulating foetal plasma. Thus at $t=0$ the "partial sodium space" of the infant is $\left(\frac{Fw}{22.2}+\frac{Pw}{7}\right)$. These values we have derived from the work of DeMarsh, Windle and Alt (1942), who found that when the cord is clamped early the plasma volume of the foetus is 4.5 per cent of body weight $\left(\frac{Fw}{22.2}\right)$. They also found that on the average 107 ml. of blood (haematocrit 51 per cent) was prevented from entering the foetus by early clamping of the cord. The placenta would not be completely emptied of blood by uterine contraction, so we have assumed that 125 ml. remains in the placenta in an average case.

The average placental weight in our series was 435 grams, thus the plasma volume in the placenta (61.25 ml) is approximately one-seventh of the placental weight.

Once diffusion out of the plasma occurs, the "partial sodium space" is increased. The correcting factor was evolved by plotting the infant plasma concentrations of Na^{24} obtained at birth (after normalizing to a standard value) and the levels found an hour later, when diffusion had occurred to the extracellular spaces of the infant (Fig. 3). The times were related to the time of injection. A newborn infant plasma concentration curve having been plotted, the curve was extrapolated back to $t=0$. The arbitrary value of 7 per cent foetal weight was then assigned to the "partial sodium space" of the infant at $t=0$, since $\left(\frac{Fw}{22.2}+\frac{Pw}{7}\right)=\frac{7Fw}{100}$ for infants at term, as an average. It was found that for $t=60$ the "partial sodium space" was 15.5 per cent of foetal weight.

One infant suffered from an inoperable myelocele but was otherwise in good health, and from it a series of specimens were taken over 4½ hours (Cox, Chalmers and Ward, 1952). The resulting curve again showed evidence of the double exponential form, but in this case the "fast" and "slow" components were each about 10 times slower than the corresponding ones in the adult. It should be observed that the infant's circulation time is nearly 10 times slower than the adult's (Windle, 1940), hence diffusion out of the plasma to the extracellular space is likely to be slower in attaining equilibrium. Flexner, Wilde, *et al.* (1947) measured the sodium space in 3 infants by assaying the concentration of Na^{24} per ml./plasma, 2½–3 hours after intravenous injection of Na^{24}. The average sodium space was 43.5 per cent of body weight. A similar method was used by Perley *et al.* (1951) and the times of sampling were from 1 hour 40 minutes to 4 hours 29 minutes, and the range of values between 28.2 and 49.8 per cent of body weight for infants up to a week old. The latter authors conclude that, in infants, the volume of fluid with which sodium exchanges readily may be approximated at any time between 1 hour 40 minutes and 4½ hours after the Na^{24} has been injected intravenously.

In our experiments the Na^{24} was transferred to the foetal plasma by the placenta from maternal plasma. Numerous changes take place in the physiology of the child shortly after birth. The most important of these changes are concerned with the circulation of the blood and with respiration. Any changes in cardiac output shortly after birth, or in the circulation time,

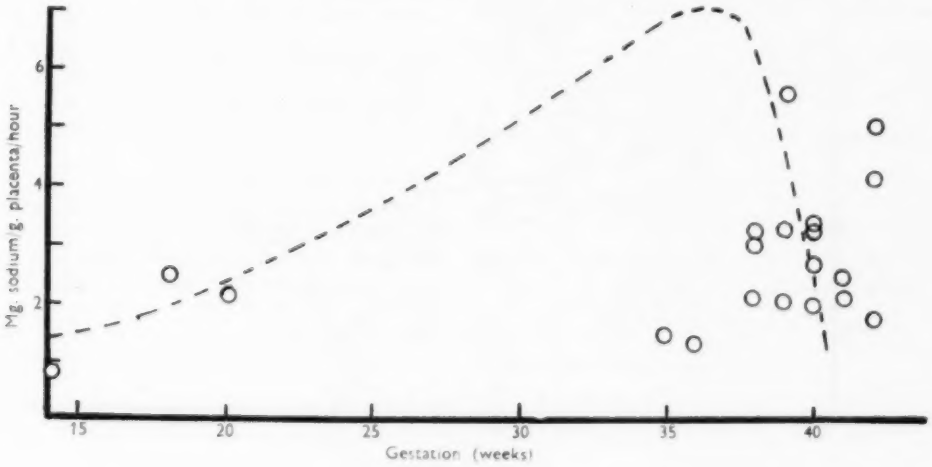

FIG. 5

The transfer of sodium across the human placenta, 20 normal cases.

– – – – = curve shown by Flexner, Cowie *et al.* (1948).

might alter the diffusion rates of sodium in the newborn infant compared with the rates *in utero*. In view of this it seems justifiable to utilize the data obtained within an hour of birth in our own experiments. We have plotted the composite data obtained by Flexner *et al.*, Perley *et al.*, and ourselves (Fig. 6). It is seen that the values for sodium space in newborn infants show considerable variations, and that the values found for the "partial" sodium space lie within the range of published data. We estimate that the maximum divergence between the values for "partial sodium space" in experiments lasting up to 15 minutes to be ± 10 per cent of the average values that we have derived for use in our calculations of sodium transfer. The earliest time that the sodium space in infants was determined by Perley *et al.* was 16 hours after birth; by Flexner *et al.* it was 1½ days after birth.

It is observed that the values found by Flexner *et al.* fall in the higher range of values for sodium space. Therefore our determinations for Na^{24} transfer through the placenta are proportionately lower than the values calculated by Flexner *et al.* The use of a particular value for the sodium space for all cases having the same time interval after injection into the maternal plasma allows strict comparison between those cases. The cases of Flexner *et al.* are strictly comparable with each other, since these workers attempted to give the injection 30 minutes before the time of delivery, thus the diffusion occurring throughout their series of infants was comparable.

The quantity of sodium transferred/gram/placenta/hour is from 1.3 to 5.5 mg. with a mean value of 2.8 mg. when calculated using our expression for the foetal sodium space. This amount of sodium crossing the placenta is many hundred times larger than is required for foetal growth. With a foetus of average size, 3 kg., and a placenta of 450 g., the quantity transferred at 2.8 mg./g. placenta/hour is 1.26 g./hour or 30 g./day.

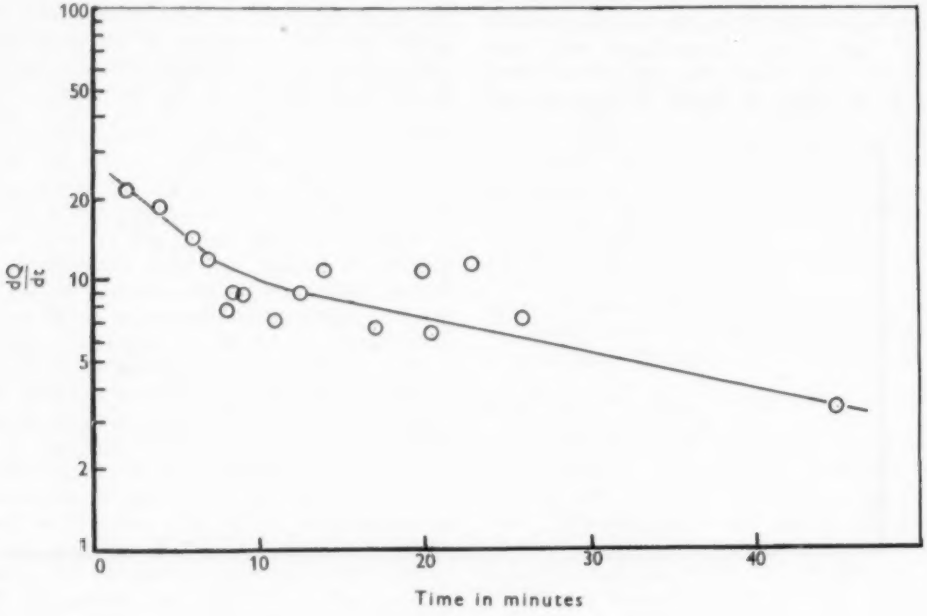

FIG. 6

The rate of transfer of Na^{24} across the human placenta $\left(\frac{dQ}{dt}\right)$, 16 normal cases.

In the previous paper (Cox and Chalmers, 1953) it was reported that in a normal pregnant woman about 40 per cent of the plasma sodium diffused out of the blood every minute. This approaches a diffusion across the vascular wall of 10 kg. of NaCl per day. The exchange of sodium with some other body fluids takes place at a very much slower rate. These fluids are the cerebrospinal fluid and aqueous humour of the eye (Visscher and Carr, 1944; Wang, 1948) and the amniotic fluid (Vosburgh *et al.*, 1950). These fluids are not nutrient in function, and the blood supply to the membranes lining the cavities in which these fluids circulate is not rich. It is possible that the exchange of sodium across a membrane is proportional to the rate of blood supply to the membrane. Certainly there is a free blood supply to the placenta, and the quantity of sodium crossing the placental membrane in each direction is much greater than can be explained by the demands of foetal growth.

Summary

(1) Isotonic NaCl labelled with Na^{24} was injected intravenously in 20 pregnant women shortly before the time of delivery.

(2) Measurements were made of the quantity of Na^{24} that had been transferred to the foetus.

(3) The quantities of sodium transferred were on an average 450 times greater than are needed for the growth increase of the foetus at the particular gestation period.

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THE EFFECT OF PRE-ECLAMPTIC TOXAEMIA ON THE EXCHANGE OF SODIUM IN THE BODY AND THE TRANSFER OF SODIUM ACROSS THE PLACENTA, MEASURED BY Na^{24} TRACER METHODS

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THE use of radio-active tracer substances in the investigation of diseased states is now well established. This method was applied to the investigation of placental transfer by Flexner *et al.* (1948) and by Cox and Chalmers (1953 a, b). Most of these studies related to the diffusion of sodium to the extracellular space, and the transfer of sodium across the placenta in normal cases. The former authors observed one case of pre-eclamptic toxaemia, and found that the placental transmission of sodium was half that of normal cases at the same period of gestation. The present work is based on a series of normal cases already reported (Cox and Chalmers, 1952 b), and an almost equal number of cases of toxaemia, in order that a controlled assessment of the effect of the disease may be made.

METHOD

A tracer dose of Na^{24} in isotonic sodium chloride was injected intravenously to the mother, shortly before delivery. The concentrations of maternal and foetal plasma radio-activity were assayed and the quantity of radio-active isotope transferred to the foetus calculated. The details of method are recorded elsewhere (Cox and Chalmers 1953 a, b).

Several groups of patients were used.

1. *Normal cases:*
   - (*a*) Delivered by Caesarean section without labour (mainly cases of repeat section for contracted pelvis) . . . . . 9 cases
   - (*b*) Delivered spontaneously after normal labour (including one case of twins) . . . . . 6 cases
   - (*c*) Delivered with forceps under anaesthesia after normal labour 2 cases
   - (*d*) Undelivered . . . . . 2 cases
2. *Cases with pre-eclamptic toxaemia:*
   - (*a*) Delivered by Caesarean section without labour . . . . . 9 cases
   - (*b*) Delivered spontaneously after normal labour (including one case of twins) . . . . . 8 cases
   - (*c*) Delivered with forceps under anaesthesia after normal labour 3 cases
3. *Other cases:*
   - (*a*) Pregnancy complicated by hydramnios in labour . . . 3 cases
   - (*b*) Normal third stage of labour . 2 cases
   - (*c*) Early pregnancy terminated by abdominal hysterotomy . . 3 cases

Broadly, the cases fall into four main groups, Caesarean section and vaginal deliveries in normal and toxaemic patients respectively.

RESULTS

The maternal plasma concentrations of Na^{24} were plotted against time. The curves drawn through these points, when analyzed in the way

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described previously (Cox and Chalmers 1953 a), showed two exponential components, the equation relating the coefficients of these components being

$$Cp—C\infty = \alpha_1 e^{-\beta_1 t} + \alpha_2 e^{-\beta_2 t}$$

The coefficients of each case were determined, and it was found that, while the values ranged about the mean for the whole series, a division could be made into two groups. The first group comprised:

2 cases of normal pregnancy at term, not in labour;

2 cases of early pregnancy at the time of performing hysterotomy;

3 cases of hydramnios, during labour;

8 cases of pre-eclamptic toxaemia (with a normal value for $\frac{dQ}{dt}$: see later) at the time of delivery.

The second group comprised:

19 cases of normal pregnancy at term, at the time of delivery;

1 case of early pregnancy at the time of performing hysterotomy;

11 cases of pre-eclamptic toxaemia (4 with normal $\frac{dQ}{dt}$ and 7 with low $\frac{dQ}{dt}$: see later) at the time of delivery.

One case of pre-eclampsia is excluded from either group because a second exponential component was not observed.

In the calculation of placental transfer of sodium, 8 cases of the second group showed a low value for $\frac{dQ}{dt}$; 7 patients had toxaemia, and the 8th was a normal case where the foetus became distressed during labour. These cases are examined separately, as Group 2b.

The coefficients are displayed in Table I, and the plasma concentration curves are shown in Fig. 1.

The average values for the rates of diffusion have been calculated in each group, and are shown in Table II.

Perusal of Tables I and II reveals that the coefficient β_2 has a higher value in Group 2b; that is, the second exponential component has a shorter half-life. Because of this a greater proportion of sodium diffuses in and out of the

TABLE I

$$Cp-C_\infty = \alpha_1 e^{-\beta_1 t} + \alpha_2 e^{-\beta_2 t}$$

Group	Cases	C_∞	α_1	β_1	α_2	β_2
1	2 normal pregnancy not in labour 8 pre-eclamptic toxaemia at delivery 3 hydramnios and 2 early pregnancy (hysterotomy)	0.147	0.69	0.57	0.172	0.0945
2a	18 normal pregnancy at delivery 4 pre-eclamptic toxaemia at delivery 1 early pregnancy (hysterotomy)	0.215	0.646	0.57	0.138	0.076
2b	7 pre-eclamptic toxaemia at delivery 1 normal labour with foetal distress	0.186	0.706	0.707	0.108	0.1212
3	3 normal pregnancy not in labour	0.306	0.404	0.521	0.289	0.0702
4	17 normal human	0.20	0.67	0.46	0.13	0.046
5	1 normal human	0.29	0.53	0.58	0.18	0.064

Groups 1, 2a, 2b: Our experiments.

Group 3: Values obtained from published graph of Flexner *et al.* (1948).

Group 4: Values from published data (Fauvert and Loverdo, 1950).

Group 5: Values from published data (Burch *et al.*, 1947).

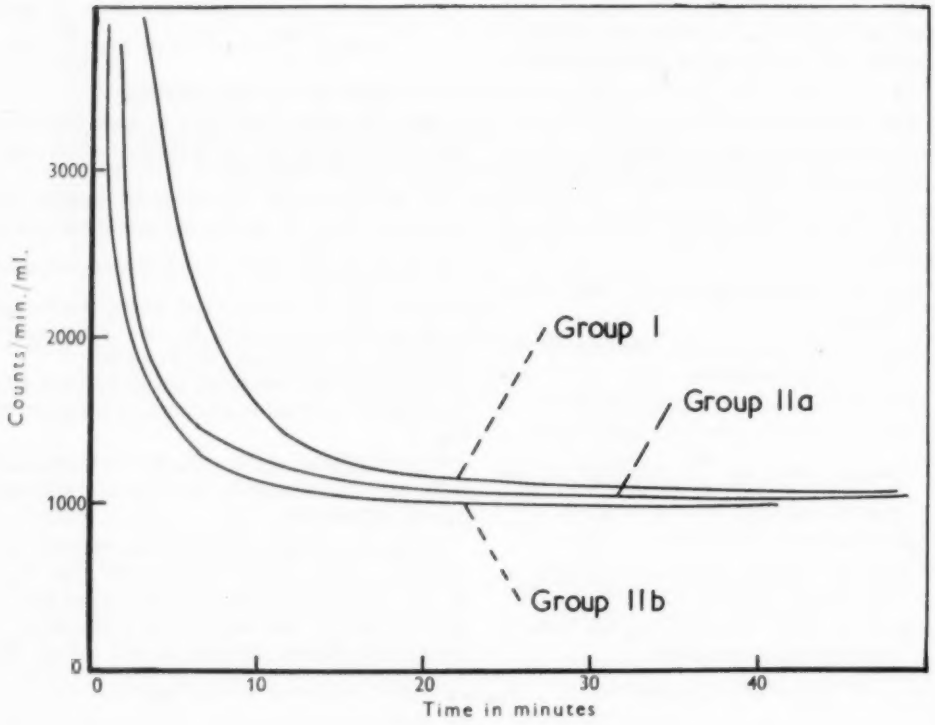

FIG. 1

Average plasma concentration curves for the 3 groups of cases.

vascular bed every minute in the cases of this group. The precision of our experimental results does not allow us to state with certainty whether this is a complete representation of the exchanges of sodium.

The sodium space was calculated from the maternal plasma concentration of Na^{24} after equilibrium was attained. The results are displayed in Table III, and Fig. 2, and may be compared with the results in normal cases previously published (Cox and Chalmers 1953a). The average sodium space in pregnant women at term is 27.9 ± 5.60 per cent body weight and in pre-eclamptic toxaemia it is 30.5 ± 6.75. Perley, Forbes and Pennoyer (1951) found the average sodium space in adult males to be 25.2 ± 4.02 per cent body weight.

The pregnant woman appears to have a higher

TABLE II

	Group 1	Group 2a	Group 2b
Percentage of sodium in interstitial fluid	85.2	78.4	70.6
Percentage of total plasma sodium diffusing out of vascular bed per minute	40.2	38.0	51.2
Percentage of total interstitial fluid diffusing into vascular bed per minute	6.9	10.5	21.4

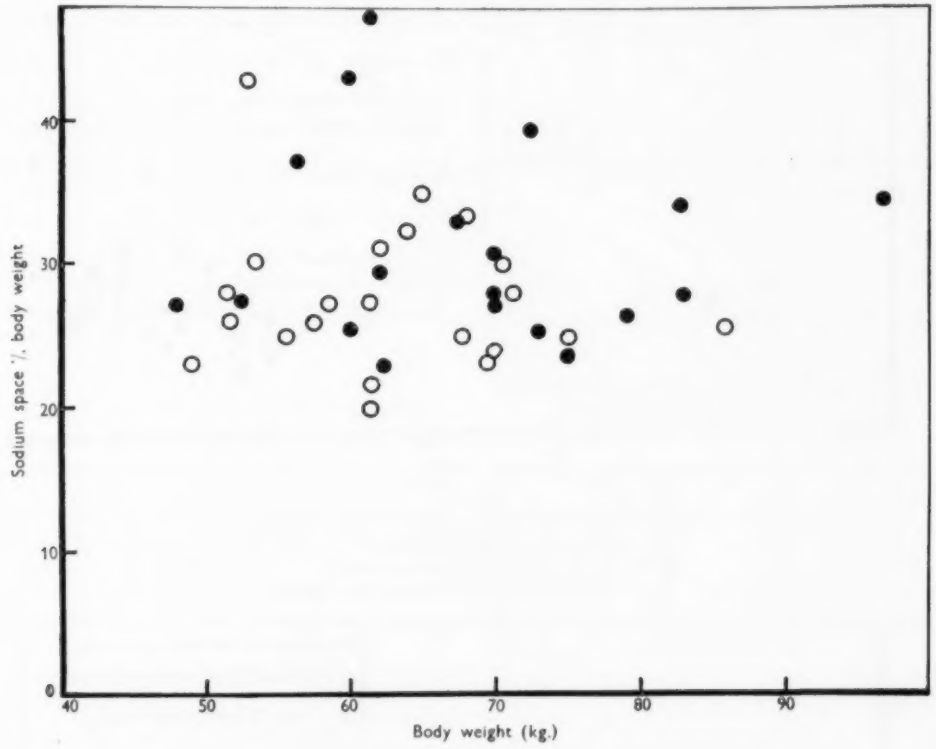

FIG. 2
Sodium space in pregnancy.
○ = Cases of normal pregnancy.
● = Cases of pre-eclamptic toxaemia.

sodium space in proportion to body weight than non-pregnant individuals, and the effect of pre-eclamptic toxaemia is to increase still further the sodium space. Most of the patients with pre-eclamptic toxaemia had clinical oedema, but in only 4 cases was the oedema severe.

Most of the patients with toxaemia had been given a diet without added salt. Unless the diet had been strictly maintained for at least a week, we did not regard the patient as salt-deprived. The sodium spaces of those cases where effective salt deprivation took place were in the higher range of values.

The placental transmission of sodium, 2.3 mg./g./placenta/hour, is on the average lower in toxaemia cases. The value for normal cases is 2.8 mg. (Cox and Chalmers, 1953b). There is not a striking difference, however, such as can be seen in the calculated instantaneous rate of transmission, $\frac{dQ.}{dt.}$

The validity of this formula

$$\int_0^t dQ = KA\,(Cm\text{-}Cf)\left(\frac{Pw}{7} + \frac{Fw}{22.2}\right)(Sp.)dt$$

has been discussed in the previous paper.

K = placental permeability.
A = area of placenta (given as weight g.).
Cm = maternal plasma concentration of Na^{24}.
Cf = foetal plasma concentration of Na^{24}.
Pw = placental weight (g.).
Fw = foetal weight (g.).
Sp = correcting factor for diffusion to foetal extracellular space.

TABLE III

Case	Severity of disease	Method of delivery	Age	Gravidity	Gestation (weeks)	Weight (kg.) antenatal	Sodium space per cent of body weight	Infant weight (kg.)	Plac wei (g
3	Severe	C.S.	22	1	35	82.75	33.9	2.075	35
12	Mild	C.S.	29	1	43	79.0	26.1	4.12	43
18	Severe	Normal	37	4	38	60.0	25.4	2.64	35
19	Severe	C.S.	23	1	38	97.0	34.3	2.75	40
23	Mild	Normal	28	3	42	75.0	23.3	2.19	25
24	Mild	C.S.	29	3	40	73.0	25.1	3.26	37
26	Mild	Normal	25	1	40	61.5	47.0	2.34	45
27	Mild	Normal (Twins)	25	2	36	72.5	39.3	2.93 1.44	36 24
30	Mild	C.S.	28	2	41.5	91.5	23.7	4.95	81
31	Severe	Forceps	27	1	38.5	60.0	42.8	3.05	60
33	Mild	C.S.	46	1	41	70.0	27.8	3.26	45
35	Severe	C.S.	26	1	39	56.5	37.3	2.50	41
37	Severe	Forceps	37	1	37	67.5	32.9	1.86	41
41	Mild	Normal	23	1	40	52.5	27.4	3.10	60
42	Severe	C.S.	25	1	35	63.5	22.6	2.55	51
44	Mild	Normal	34	3	38	83.0	27.6	3.25	42
45	Severe	C.S.	27	1	36	62.0	29.2	2.48	32
46	Mild	Forceps	38	1	41	48.0	27.2	2.76	37
47	Mild	Normal	28	2	39	70.0	26.9	3.08	38
48	Mild	Forceps	21	1	38.5	70.0	30.5	3.00	45

: III

Placenta weight (g.)	Counts/ min./ml. maternal plasma normalized	Counts/ min./ml. foetal plasma normalized	Correcting factor for average maternal plasma concentration	Time (min.)	Sodium transferred mg./g. placenta/hr.	$\frac{dQ}{dt}$	Safety factor
350	1186	411	1.50	12	1.88	4.76	309
430	1984	719	1.76	6	4.58	15.3	201
356	1020	600	1.57	28	1.87	2.67	274
400	9780	550	1.77	7		74.9	
256	1300	223	1.57	6.5	2.06	4.26	271
376	1237	430	1.56	9	3.01	8.07	388
453	1395	564	1.56	9	2.41	7.29	521
362	3108	273	1.64	3.5	1.66	21.1	210
248	1000	377	1.52	39	0.89	2.66	157
810	1120	500	1.72	14	1.89	2.10	345
600	1077	749	1.52	39	1.47	7.47	315
453	1299	524	1.54	10	2.67	8.82	414
410	2700	543	1.76	6.5	1.64	16.9	295
412	1209	647	1.55	9.5	2.84	4.28	670
600	1175	410	1.57	6	2.95	7.72	637
510	1311	339	1.78	9	1.32	10.6	264
426	1174	744	1.57	8	5.55	4.76	786
328	1127	349	1.62	23	1.11	5.63	150
370	1066	814	1.33	30	2.73	2.49	407
386	1149	866	1.57	13	4.48	2.58	616
450	1095	726	1.59	26	2.03	4.82	332

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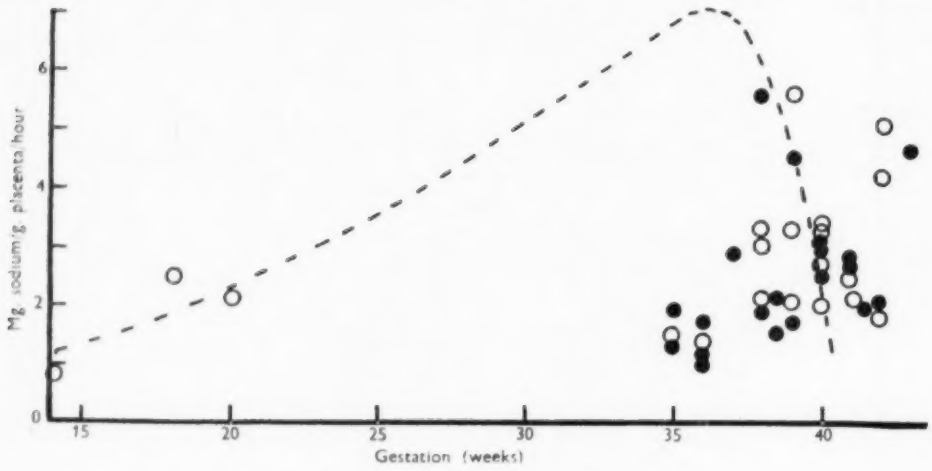

FIG. 3

The transfer of sodium across the human placenta.

○ = Cases of normal pregnancy.
● = Cases of pre-eclamptic toxaemia.
– – – – = Curve shown by Flexner *et al.* (1948).

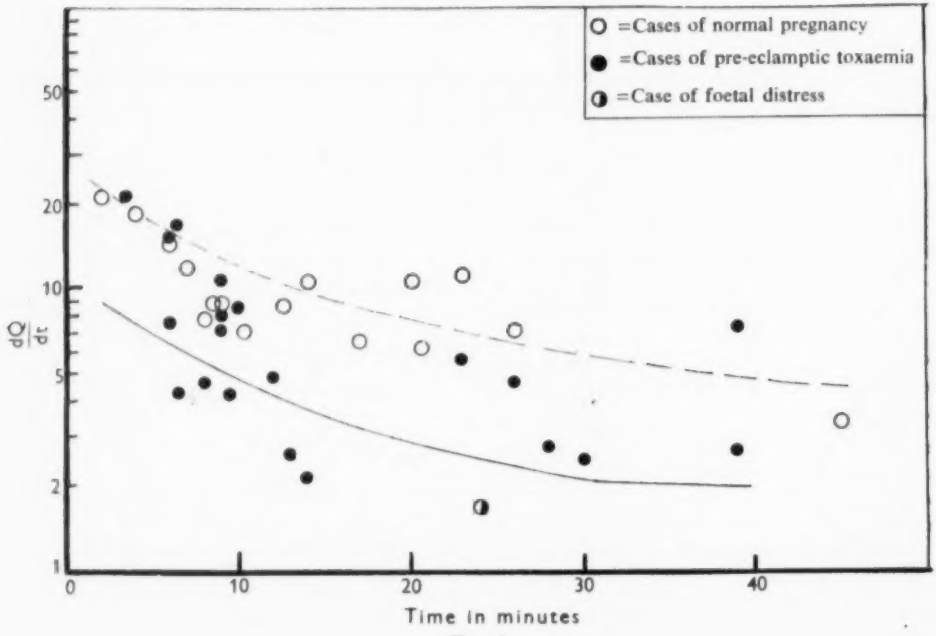

FIG. 4

The rate of transfer of Na^{24} across the human placenta $\left(\frac{dQ}{dt}\right)$

No significant difference was observed in the values for $\frac{dQ}{dt}$ according to the method of delivery. Cases of Caesarean section and spontaneous delivery are distributed evenly throughout the series.

The findings of a group of 8 cases (2b) with a low value for $\frac{dQ}{dt}$ suggests that a lowered placental permeability may be the cause. These same 8 cases have an increased rate of diffusion of sodium in and out of the maternal plasma per minute.

Discussion

The "sodium space" is a theoretical space, corresponding almost exactly with the extracellular water content of the body. While there is a fairly wide range of values for the sodium space in normal pregnant women and in those with pre-eclamptic toxaemia, the average value is higher in the latter group. Most of these patients showed a trace of clinical oedema, but of the 4 patients with the most severe oedema (3 with ascites seen at Caesarean section) 2 had very high, and 2 had normal sodium spaces. It was observed that those patients who had had a salt-restricted diet for some days also had high values for the sodium space. Under resting conditions in hospital these patients appeared to have made slight improvement in their condition, the symptoms and signs of toxaemia having become less severe. In most cases oedema had diminished, and was barely detected at the time of delivery. One would have expected that the disappearance of oedema would lead to a lower sodium space. This apparent paradox may be explained by the sodium adsorption on bone theory, briefly discussed in the previous paper (Cox and Chalmers, 1953a). When the period of salt restriction is long enough to deplete the body reserves, the sodium adsorbed on bone is diminished and the plasma and extracellular fluids are maintained in normal tonicity of sodium. On the injection of sodium to a patient in this partly deprived state, the excess sodium is withdrawn from the circulating fluids quickly, and re-adsorbed on the bone.

The diffusion rates out of the plasma confirm this supposition. The salt-deprived cases showed

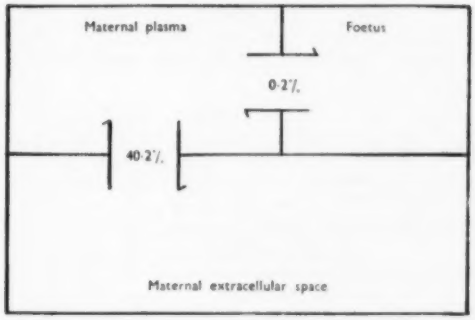

Fig. 5

Diagram showing the percentage of plasma sodium exchanged per minute. Group 1.

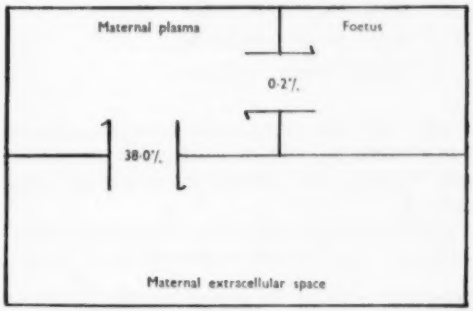

Fig. 6

Diagram showing the percentage of plasma sodium exchanged per minute. Group 2a.

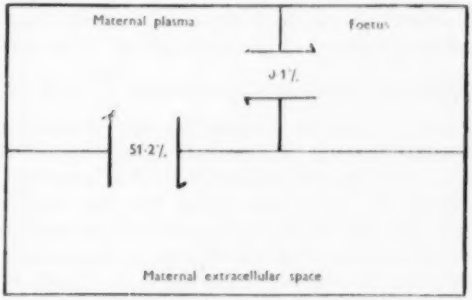

Fig. 7

Diagram showing the percentage of plasma sodium exchanged per minute. Group 2b.

TABLE IV

	Toxaemia		
	7 cases "low $\frac{dQ}{dt}$"	14 cases "normal $\frac{dQ}{dt}$"	16 cases normal pregnancy
Severity of disease:			
Severe	2	5	
Mild	5	9	
Method of delivery:			
Caesarean section	3	4	
Forceps delivery	0	3	
Normal delivery	4	7	
Salt deprived diet	4	6	1
Gravidity:			
Primigravidae	3	12	
Multigravidae	4	2	
Age of mother, average years	28	28	
Gestation, average weeks	39	39	39
Infant weight, average kg.	2.93	2.86	3.12
Placenta weight, average g.	462	410	422

a very fast first component, or an accelerated "fast" diffusion rate, indicating that the sodium was leaving the plasma more rapidly than normal.

On the average the values for sodium transferred are less than the values found in normal pregnancy. Using the expression for $\frac{dQ}{dt}$, however, the cases of toxaemia separate into two well-defined groups. The first group of cases show no deviation from normal cases. The second group of 7 cases have values of $\frac{dQ}{dt}$ of one-half or one-third those of normal cases delivered after the same time interval. The only other case with a similar value for $\frac{dQ}{dt}$ was one where the foetus became severely distressed towards the end of a normal labour. These 8 cases were examined carefully to find some correlating factor. It was found that the average value for the second component of the plasma concentration curve was higher in these cases. That is, the "slow" diffusion rate of sodium out of the plasma is accelerated. This means that a greater proportion of sodium diffuses in and out of the vascular bed per minute.

These changes were depicted diagrammatically, both the plasma diffusion coefficients and the values for $\frac{dQ}{dt}$ being used. It is seen that while there is greatly increased sodium transfer between the plasma and the extracellular fluid by both "fast" and "slow" rates, the transfer to the foetus is halved. We are not able to infer from our experimental results which effect is primary, or if the effects are interrelated.

The remaining cases of toxaemia, so far as diffusion rates are concerned in the mother and across the placenta, appear the same as normal cases. We append the details of the search for correlating factors, and observe that there is another factor which, had the series been larger, might have proved a significant one. Of the "low $\frac{dQ}{dt}$" cases there was a higher proportion of multigravidae, and all these had previously suffered from toxaemia.

SUMMARY

(1) Measurements were made of the maternal plasma concentration curves and of the foetal plasma concentration after intravenous injection of isotonic saline labelled Na^{24} in the mother.

(2) Anomalous plasma concentration curves were found in certain of the toxaemic cases.

(3) A diminished rate of transfer of sodium across the placenta was observed in the cases with anomalous plasma concentration.

(4) A search for correlating factors showed that all patients with recurrent toxaemia had a diminished transfer of sodium across the placenta.

We wish to thank the Medical Research Committee of the United Liverpool Hospitals for a grant to defray the cost of materials; Professor T. N. A. Jeffcoate for his help and encouragement; the visiting obstetricians to the Liverpool Maternity Hospital, Walton Hospital, and Mill Road Maternity Hospital, for permission to make observations on their cases; and Dr. J. K. P. Perera for taking many of the specimens.

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THE TRANSFER OF SODIUM TO THE AMNIOTIC FLUID IN NORMAL AND ABNORMAL CASES, DETERMINED BY Na^{24} TRACER METHODS

BY

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MEASUREMENTS of the quantities of sodium and water transferred to the amniotic fluid using tracer methods were made by Vosburgh, *et al.* (1950). They found that 34.5 per cent of the water and 6.9 per cent of the sodium are replaced every hour in cases of normal pregnancy.

In the course of experiments on placental transfer (Cox and Chalmers, 1953 a, b, c) we were able to study the transfer of Na^{24} to the amniotic fluid in 9 cases of normal pregnancy when the child was delivered by Caesarean section, and in 2 cases of normal pregnancy when a non-viable foetus was delivered by hysterotomy. In addition we investigated the transfer of Na^{24} to the amniotic fluid in 3 cases of hydramnios.

METHODS

In 11 cases of normal pregnancy an injection of isotonic NaCl labelled with Na^{24} was given just before performing Caesarean section or hysterotomy. The details of technique are recorded elsewhere (Cox and Chalmers, 1953 a, b). After incising the uterus the liquor was withdrawn with an aspirator and the quantity measured. It was estimated that about 300 ml. were spilt in each case, so this arbitrary figure is added to the measured value in each case. These specimens were later assayed for radio-activity using a G.M. M6 liquid counter.

In 3 cases of hydramnios labour was to be induced for obstetrical reasons, the method used being puncture of the membranes. In each case the foetus was living, but suffering from gross malformations incompatible with separate existence (anencephalus in 2 cases and large cranial and spinal meningoceles in the third). In 2 cases the amniotic cavity was tapped by inserting a large bore spinal needle through the linea alba below the umbilicus. A rubber tube was connected to this needle, and the liquor allowed to drip slowly away, the rate being approximately 40 drops per minute. The tracer substance was injected intravenously and specimens of the liquor were obtained at intervals. In one case this slow drainage of liquor induced labour. In the other case, as no uterine contractions were observed, 1,800 ml. of amniotic fluid were withdrawn with a syringe, and an hour later a similar quantity. Labour then followed. In the third case, instead of tapping the amniotic cavity through the abdominal wall the membranes were punctured with the Drew-Smythe catheter, and 1,080 ml. of liquor withdrawn 2 hours after giving the radio-active injection. No further sample was obtained in this case, and as labour did not follow for 2 days the radio-active decay of Na^{24} vitiated further assay of plasma samples.

The infants in each case of hydramnios were born with strong heart beats, but no respiratory movements occurred. It is assumed that, so far as the placental circulation was concerned, these infants behaved as normal.

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TABLE I

Case No.	Type of case	Delivery	Gestation weeks	Time injection–delivery minutes	Counts /min./ml. maternal plasma (average)	Counts /min./ml. liquor	Sodium transferred /ml. liquor /hour mg.	Per cent of sodium of liquor renewed/ hour	Estimated volume of liquor ml.	Total sodium transferred /hr. mg.
1	Normal	C.S.	40	10	429	14	0.645	23.0	600	387
2	Normal	C.S.	40	5.5	387	2.4	0.325	11.6	990	322
3	Toxaemia	C.S.	35	10	530	36.7	1.71	61.0	720	1231
4	Normal	C.S.	38	8	1330	33	0.615	21.9	1290	793
5	Normal	C.S.	41	18	1570	74.5	0.548	19.6	330	181
6	Normal	C.S.	40	23	674	12.9	0.146	5.2	1500	219
7	Normal	C.S.	38	15	1020	48.1	0.622	22.2	390	243
24	Toxaemia	C.S.	40	7	997	27.9	0.789	28.1	1350	1065
25	Psychiatric	Hysterotomy	14	14	1179	14.4	0.172	6.1	100	17
39	Cardiac	Hysterotomy	20	20	951	12.9	0.134	4.8	255	34
42	Toxaemia	C.S.	35	6	627	3.9	0.205	7.3	630	129
34	Hydramnios	Vaginal	35	5	1225	1.8	0.0582	2.1	5000	291
				10	1082	11.3	0.142		4964	701
				26	938	3.7	0.0300	1.1	4923	147
				36	840	4.8	0.0314		4886	153
				47	756	9.0	0.0501	1.8	4845	243
				136	624	21.4	0.0500		4520	226
				162	576	26.6	0.0562		4430	249
				189	480	29.7	0.0650		4400	286
36	Hydramnios	Vaginal	36	10	1190	4.7	0.0780	2.8	5000	390
				18	952	7.8	0.0902		4550	410
				28	848	13.0	0.109		4100	447
				38	706	15.1	0.110	3.9	3650	402
				48	651	21.8	0.138		3200	442
				63	579	30.1	0.163		3190	520
				98	504	42.5	0.169		2290	387
				145	440	71.7	0.222	7.9	1400	311
				753	400	308	0.203		1400	
38	Hydramnios	Vaginal	40	124	425	26.3	0.099	3.5	5000	495

Results

In the cases with a normal volume of liquor amnii, the sample examined being obtained at Caesarean section or at hysterotomy, calculations were made according to the method of Vosburgh *et al.* (1950). The quantities of Na^{23} and Na^{24} transferred to the liquor are in the same ratio as that found in the plasma.

$$\frac{\text{Na amf}^*}{\text{Na amf}} = \frac{\text{Na mp}^*}{\text{Na mp}}$$

The value Na mp = 3.3 mg./ml.
(Peters and van Slyke, 1931.)

$$\text{Therefore Na amf} = \frac{3.3\ \text{Na amf}^*.}{\text{Na mp}^*}$$

The average percentage of amniotic fluid sodium exchanged per hour was 19.1 per cent in normal cases and 2.8 per cent in cases of hydramnios. The individual measurements on normal cases and the serial measurements on abnormal cases are displayed in Table I.

Discussion

Our results are of a similar order of magnitude to those of Vosburgh *et al.*, except that 2 cases of toxaemia showed an increased rate of transfer of Na^{24} to the liquor amnii. In our series 19.1 per cent of sodium of the amniotic fluid was renewed per hour, assuming the sodium content to be 2.8 mg. per ml. (Needham, 1931). Vosburgh *et al.* found an average value of 6.9 per cent but included a higher proportion of cases in the early weeks of gestation, most of which showed a lower percentage transfer. Our results suggest that equilibrium is reached between radio-active sodium in the liquor and in the maternal plasma in about 5.2 hours in normal cases.

Where hydramnios exists, a slower rate of transfer is observed. Taking the average values found at the beginning of each experiment, at the first samplings of the liquor 2.8 per cent of the sodium is exchanged in one hour. This indicates an equilibrium point of about 36 hours. The volume of liquor in the case of hydramnios was estimated to be approximately 5 litres and the volumes withdrawn were measured. This makes it possible to calculate the total quantity of sodium transferred to the liquor per hour.

The average total sodium transferred in normal cases at term is 0.5 gm. per hour, and is 0.35 gm. per hour (averaging the multiple readings) in cases of hydramnios. The suggestion is therefore made that the quantity of sodium transferred to the liquor in any case at term is approximately the same, the quantity of liquor into which the transfer takes place being a variable factor.

The observations do not permit us to speculate on the mode of formation of amniotic fluid, except to say that it is unlikely that foetal urine contributes appreciably to its sodium content. In 3 cases a specimen of liquor obtained 5 minutes or less after injection of Na^{24} into the maternal circulation contained a measurable quantity of Na^{24}. It is unlikely that urine secreted in this period by the foetal kidneys would have reached the bladder and been voided into the liquor in every case.

Summary

(1) In cases of normal pregnancy and in cases of hydramnios measurements were made of the concentration of Na^{24} in the amniotic fluid at intervals after intravenous injection of NaCl labelled Na^{24} had been given to the mother.

(2) The percentage of sodium in the amniotic fluid exchanged every hour is 19.1 in nomal cases, and 2.8 in cases of hydramnios.

(3) The total quantity of amniotic fluid sodium exchanged per hour is of the same order of magnitude in normal cases at term, and in cases of hydramnios.

(4) Na^{24} appears in the amniotic fiuid within 6 minutes of its intravenous injection in the mother.

We wish to thank the Medical Research Committee of the United Liverpool Hospitals for a grant to defray the cost of materials; Professor T. N. A. Jeffcoate for permission to use 2 cases under his care at Mill Road Maternity Hospital; and Dr. Kenneth Baker, M.R.C.O.G., for his co-operation with these cases.

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TABLE

Case No.	Method of delivery	Time injection to delivery of child (min.)	Time third stage of labour (min.)	Maternal plasma radio-activity at delivery of child Counts/ml./min.	Probable error per cent ±	Cord plasm radio-activi Counts/ml. min.
1	C.S.	11	2	333	1.6	95
3	C.S.	12	5½	334	1.3	109
4	C.S.	12½	1½	853	1.0	388
5	C.S.	20½	2	720	1.3	355
6	C.S.	26	2	490	1.0	205
7	C.S.	20	5	711	1.2	80
9	Normal	A.D.	7*	—	—	—
11	Normal	6	11	650	0.9	195
12	C.S.	6	1	635	1.3	230
13	Forceps	24	1	387	1.7	336
14	Normal	4	6	578	1.3	164
16	Normal	A.D.	9*	—	—	—
17	Normal	17	9	600	1.1	370
18	Normal	28	3	337	1.5	200
19	C.S.	7	2	1956	0.8	110
20	Forceps	9	1	525	1.3	246
21	Twins 1.	A.D.	95*	—	—	—
	2.	45	50	362	1.5	194
22	Normal	8	16	770	1.2	318
23	Normal	6½	29	487	1.2	83.5
24	C.S.	9	1	570	1.4	198
26	Normal	9	8	270	1.3	110
27	Twins 1.	3½	48	316.5	1.3	24.6
	2.	39	12½	192	1.6	34
28	C.S.	14	1½	463	1.3	160
30	C.S.	14	2½	290	1.9	262
31	Forceps	39	1	195	1.6	135
32	Normal	2	9	1103	1.1	280
33	C.S.	10	1	480	1.2	194
34	Normal	207	7	488	1.0	400
35	C.S.	6½	10	743	1.0	181
37	Forceps	9½	1	508	1.1	272
40	C.S.	23	3	686	1.2	271
41	Normal	6	7	470	1.6	164
42	C.S.	9	1	282	1.4	73
43	C.S.	7	1½	497	1.2	109
44	Normal	8	9	275	1.5	171
45	C.S.	23	1	668	1.1	209
46	Forceps	30	1	335	1.6	224
47	Normal	13	6	345	1.9	260
48	Forceps	26	2	380	1.5	253

C.S. = Caesarean section. A.D. = Injection made after delivery

TABLE I

ord plasma dio-activity ounts/ml./ min.	Probable error per cent ±	Maternal plasma radio-activity at delivery of placenta Counts/ml./ min.	Placental vein plasma radio-activity Counts/ml./ min.	Probable error per cent ±	Placental plasma radio-activity Counts/ml./ min.	Probable error per cent ±
95	3.6	279	156	2.2		
109	2.2	334	129	1.6		
388	0.95	790	550	0.9		
355	1.3	720	496	1.5		
205	2.0	470	296	1.2		
80	2.4	590	139	0.9		
—	—	343 ± 1.5 per cent	—	—	56.6	3.2
					150	2.2
195	2.0	360			268	2.3
230	2.2	610	289	2.0	279	1.4
336	1.8	360	307	2.1	254	2.6
164	2.4	395	300	2.0	188	2.5
—	—	256 ± 2.4 per cent	—	—	435	1.3
370	2.2	540	466	1.6		
200	2.7	337	261	1.8		
110	2.5	1140	153	3.7		
246	1.7	500	276	1.6	230	1.8
—	—	348	240	4.1		
194	2.4	348	310	2.2		
318	1.5	565	506	1.2	425	1.5
83.5	3	400	187	3.3		
198	3	570	215	2.1		
110	2.5	201	160	3.3		
24.6	3.9	192	53.5	3.5		
34	4.4	192	48.8	3.4		
160	2.2	450	275	1.3	262	2.2
262	2.0	290	159	1.6	125	2.8
135	2.2	195	144	2.1	129	1.5
280	3.0	620	418	1.4		
194	1.7	480	314	1.4	324	1.5
400	1.5	488	418	1.0		
181	1.7	595	285	1.6	348	0.9
272	1.8	508	334	1.5	449	1.1
271	2.0	650	359	1.9		
164	2.0	408	281	1.6	350	1.6
73	2.9	282	216	1.3	446	0.7
109	3.8	465	267	1.4	458	1.3
171	1.9	250	222	1.9		
209	2.3	659	315	1.9	322	1.9
224	1.9	335	239	1.4	200	1.9
260	2.6	310	201	2.4	281	2.5
253	1.5	370	290	1.4	178	2.0

er delivery of child.

* — Time from injection to delivery of placenta.

Facing p. 226

THE TRANSFER OF SODIUM TO THE PLACENTAL BLOOD DURING THE THIRD STAGE OF LABOUR DETERMINED BY Na^{24} TRACER METHODS

BY

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WHILE studying the permeability of the placenta to radio-active sodium, specimens of cord blood were taken immediately after the child was delivered (Cox and Chalmers, 1953 b, c). The first such case was delivered by Caesarean section, and the cord clamped and divided in the usual way. The placenta was undisturbed until the uterus expelled it spontaneously 4 minutes later. A specimen of cord blood (about 10 ml.) was collected in a heparinized tube and then a duplicate sample was obtained by "milking" the cord. When these specimens were assayed for radio-activity it was found that the plasma radio-activity of the second specimen was higher than that of the first specimen by nearly 60 per cent. This suggested that an active circulation persists through the placental site during the third stage of labour. The technique was therefore revised to enable us to determine whether the transfer of Na^{24} continued across the placenta after delivery of the child.

MATERIAL AND METHOD

Studies were made in 39 pregnant women, including 2 cases of binovular twin pregnancy. Each set of twins comprised one male and one female infant. Seventeen cases were delivered by Caesarean section, and 6 with forceps. The remainder, 16 cases including both sets of twins, were delivered spontaneously. Twenty patients (including 1 with twins) suffered from pre-eclamptic toxaemia, 9 being delivered by Caesarean section, 4 with forceps, and 7 spontaneously (1 twin).

In 36 of the cases isotonic saline labelled with Na^{24} was injected intravenously shortly before the expected time of delivery. The cord was clamped and divided immediately the child was delivered. Another clamp was then placed on the cord near the vulva, or when Caesarean section had been performed, near the uterine wound. This isolated a segment of cord blood which was later collected in a heparinized tube. When the placenta was expelled, a sample of blood was withdrawn with a syringe from one of the large veins on the foetal surface of the placenta. The cord was then divided at its origin on the placenta, and the organ squeezed manually to expel the foetal blood which was collected.

In those cases having an operative delivery ergometrine 0.5 mg. was injected intravenously just as the foetal head was delivered. The placenta was expelled within 1 to 5 minutes.

In 3 normal cases including 1 case of twins, the Na^{24} was injected after delivery of the child in the single pregnancies and after the delivery of the first twin. Specimens of blood were collected in the manner already described.

In all cases, serial samples of maternal blood were taken for radio-active assay. The details of this assay and the analysis of the plasma concentration curves plotted against time are recorded in previous papers (Cox and Chalmers, 1953 a, c).

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Results

In 36 of the 39 cases a higher concentration of Na^{24} was observed in samples of plasma obtained from the placental vein than in samples from the cord. In the remaining 3 cases, the concentration in the placental vein were significantly lower than in the cord. These 3 cases also showed the lowest values for the rate of Na^{24} transfer $\frac{dQ}{dt}$ given in detail in a previous paper (Cox and Chalmers, 1953c). Of these 3 cases 2 had pre-eclamptic toxaemia, and in the third case the foetus was severely distressed during labour.

When the injection was given after delivery of the child (3 cases) an appreciable concentration of Na^{24} was found in the placental blood samples.

The values found are set out in Table I and are plotted graphically.

When allowance is made for the weight of placenta, and the approximate volume of foetal plasma in the placental vessels, the rate of exchange of Na^{24} per gram of placenta per minute after delivery of the child in those cases with a second stage of a few minutes only is approximately the same as that observed prior to delivery.

Discussion

Following the delivery of the child the uterus becomes much smaller in size, containing only the placenta and a small amount of amniotic fluid. The shortening of uterine muscle fibres which occurs with this contraction and retraction might be expected to have a profound effect on the circulation of blood through the vessels of the placental site. From the amount of haemorrhage that may occur during the third stage of labour when the placenta is partly separated one infers that some circulation persists in the uterine vessels. The finding of Na^{24} in an appreciable concentration in the placental blood when it was introduced to the maternal circulation during the third stage rather goes to confirm this inference, that some circulation exists through the placental site.

According to DeMarsh, Windle and Alt (1942) the quantity of blood remaining in the placenta when the cord is clamped immediately after delivery of the child is approximately 107 ml. It is with the sodium in this blood that the Na^{24} atoms exchange during the third stage.

In the remaining 33 of the 36 cases in which the placental blood showed a higher concentration of Na^{24} than the cord blood, this higher concentration may be due to:

(1) the persistence of an active circulation in the uterus for the first few minutes of the third stage; or

(2) the exchange of Na^{24} atoms actually in the trophoblast with Na^{23} atoms in the foetal plasma in the placenta.

The persistence of an active circulation has been shown to exist in the 3 cases already described. The exchange of Na^{24} atoms from the trophoblast has also been shown to occur by Kaiser and Cushner (1951), who took a sample of placental vein blood after delivery of the placenta and a second sample 10 minutes later. This second sample in most cases showed a higher concentration of Na^{24} than the first. A similar observation on cases of hysterotomy was made by Cox and Chalmers (1953b) who measured the radio-activity of cord plasma, of exudate from the placenta (presumably placental extracellular fluid), and of minced placental tissue. The radio-activity was least in the cord plasma and highest in the placental tissue. These observations suggest that there is a concentration gradient, the Na^{24} being taken up by the trophoblast and exchanged with Na^{23} of the placental plasma and extracellular tissues. Part of the increased radio-activity of the placental plasma in the third stage may be due to this phenomenon.

In the 3 remaining cases the concentration of Na^{24} decreased by 20–50 per cent. This contrasts with the findings in the 33 cases where there was an increase of 50 per cent and the 3 cases when the increase was from zero. The 3 cases where the concentration decreased, had the lowest values for $\frac{dQ}{dt}$ (the rate of transmission of Na^{24}) found in the whole series of cases previously presented. This suggests that in some cases a different mechanism of sodium transmission is in operation.

In many cases the concentration of Na^{24} was

lower in the blood squeezed from the placenta than in the placenta vein blood. No explanation is offered to account for these observations.

When the individual cases are plotted graphically, it is seen that, while the average increase of Na^{24} concentration is approximately the same in cases of operative delivery (with ergometrine), and in cases of normal delivery (without ergometrine), the time interval between the two samples is greater in the latter case. If an active circulation persists throughout the whole third stage of labour, one might expect the increased concentration to be proportional to time. The failure to observe this continued increase suggests that the active circulation persists only for the first part of the third stage of labour, and that once the uterus has contracted and retracted the uterine circulation ceases and transfer of Na^{24} to the foetus also ceases. The time this circulation persists may be short, since the third stage in many of these cases lasted only 1 or 2 minutes, and the proportionate increase of placental blood radio-activity was as much in these as in other cases.

Summary

(1) Isotonic saline labelled with Na^{24} was injected intravenously just before delivery. Samples of placental blood taken at the end of the third stage of labour showed a higher concentration of Na^{24} than samples of cord blood taken at delivery in 33 of 36 cases. A significantly lower concentration was found in the remaining 3 cases.

(2) When the injection was made during the third stage of labour (3 cases) an appreciable quantity of Na^{24} was transferred to the placental blood.

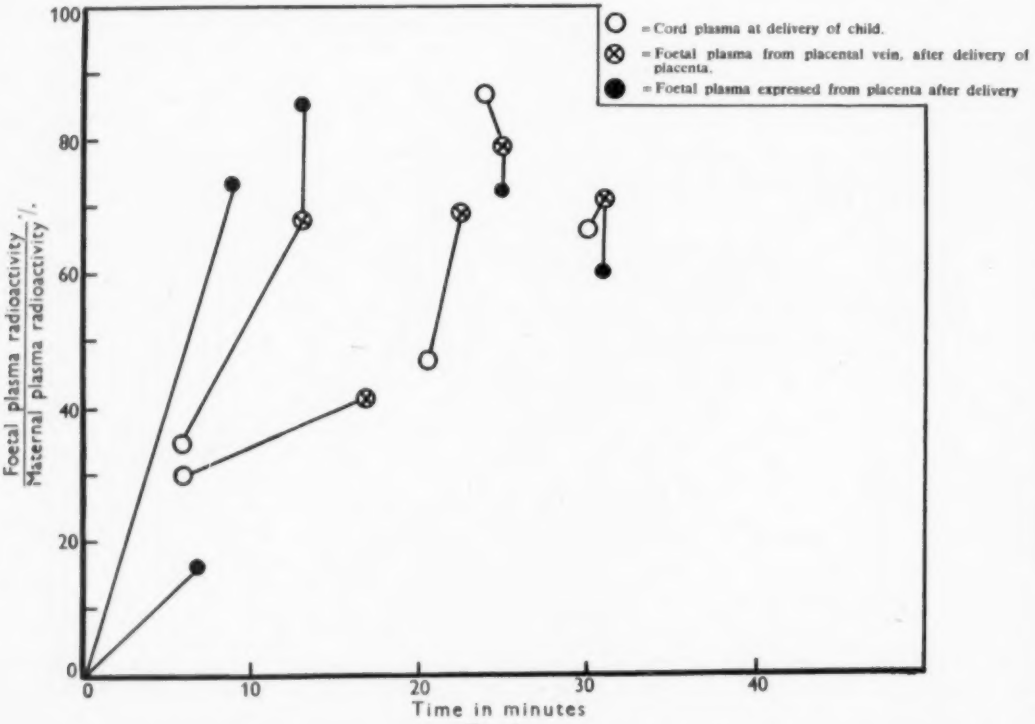

FIG. 1

Graph showing 7 examples of the 39 cases investigated, illustrating the changes taking place during the third stage of labour, in the foetal plasma concentration of Na^{24}.

(3) It is suggested that an active uterine circulation persists for the first few minutes of the third stage.

We wish to thank the Medical Research Committee of the United Liverpool Hospitals for a grant to defray the cost of radio-active materials.

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A GIANT CELL TUMOUR OF BONE IN A PSEUDOMUCINOUS CYSTADENOMA OF THE OVARY

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THE pseudomucinous cystadenoma of the ovary is, from many points of view, a remarkable tumour. It can, first, attain a far greater size than any other neoplasm of the human body. In fact, all the reports in the older literature on "Mammoth Tumours" concern this type of growth. Even if in our days of surgical enterprise tumours of 100–150 kg. are no longer seen, tumours of 10–15 kg. are by no means rare.

Secondly, in most statistics, the pseudomucinous cystadenoma figures as the most common tumour of the ovary. One-third to one-half of all true ovarian neoplasms are said to be of this variety.

Thirdly, the pseudomucin, which the tumour produces in such abundance, has proved to be interesting material. It is, for example, a rich source for blood group substances. Virus workers have found many of these cystic tumours to contain large amounts of "virus inhibitor", i.e., a substance inhibiting haemagglutination by influenza virus under certain experimental conditions.

Fourthly, there is today a tendency to eliminate from the group of proper benign neoplasms many of the lesions that have been usually classified under this heading. Some are now rather regarded as malformations (e.g., many of the haemangiomata), others as hyperplasias (e.g., the adenomata of the endocrine glands, even the myoma of the uterus), still others have moved closer to the group of the malignant tumours. The pseudomucinous cystadenoma is one of the few growths whose classification as a benign tumour remains unchallenged.

Fifthly, in spite of innumerable attempts there is still no satisfactory solution of the problem of the histogenesis of the pseudomucinous cystadenoma. Even if one believes that the histogenetic approach to tumour classification is futile, that one never can tell where a tumour came from, only what it looks like, one cannot help speculating which cells in the ovary might have given rise to this neoplasm. Then the fact remains, no cell in the ovary has any resemblance to the cells of the pseudomucinous cystadenoma. To say that metaplasia has been at work is just begging the question and explains nothing. At its best, metaplasia is a descriptive term; but it is not an explanatory one.

This leaves us with two other theories as to the origin of the pseudomucinous cystadenoma; the suggestion that it is a one-sided teratoma, and the other that it originates from Walthard cell rests. Either of these theories derives some support from the sixth and last point that makes the pseudomucinous cystadenoma a remarkable tumour, i.e., its frequent association with other neoplasms. The combination of pseudomucinous cystadenomata with teratomata, especially the so-called dermoid cysts, has long been known. One may find each ovary harbouring one of the tumours, the same ovary may contain both tumours as distinctly separate growths, or there may be only one cystic tumour which consists in varying proportions of a pseudomucinous cystadenoma and a teratoma. These observations have led to the suggestion that the pseudomucinous cystadenoma represents a teratoma, in which differentiation in only one direction, i.e., towards epithelium of the large intestine, has taken place. Further support for this idea stems from the observation that a pseudomyxoma peritonei may arise either from a pseudomucinous cystadenoma of the ovary or from an intestinal lesion, usually a mucocoele of the appendix.

The other interesting combination is that of a pseudomucinous cystadenoma and a Brenner

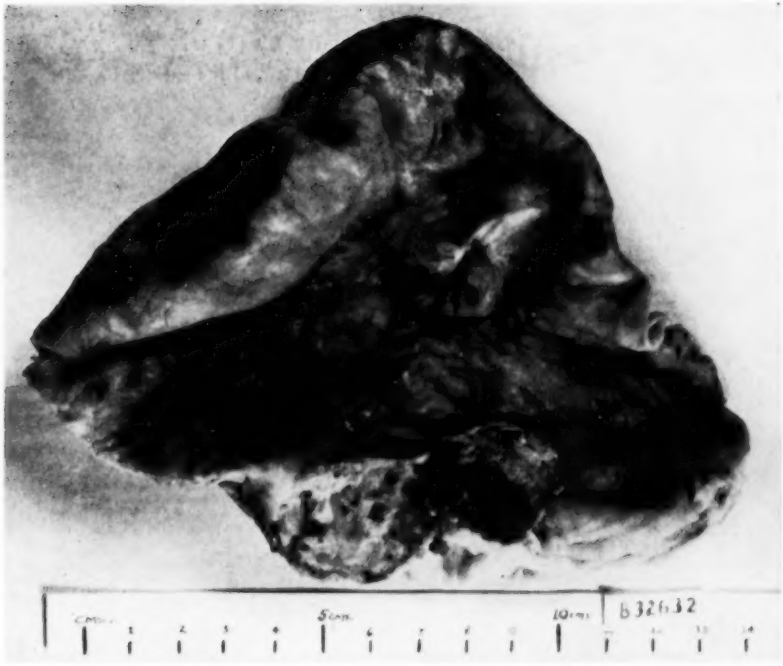

FIG. 1

Macroscopic appearance of the cystic tumour. Note the solid nodule just above the ruler.

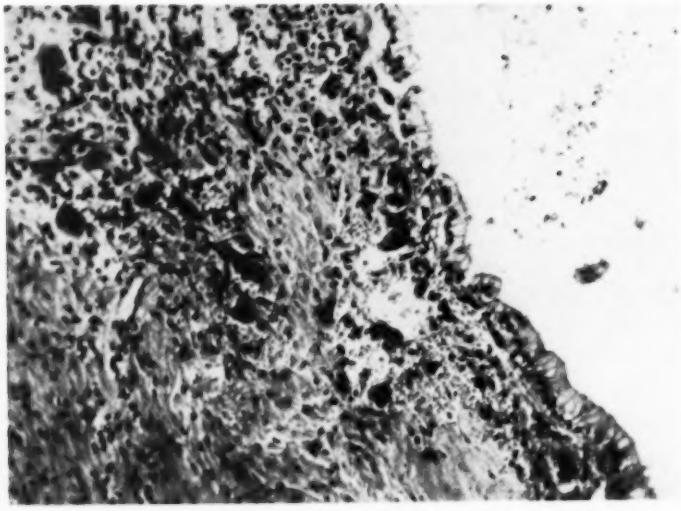

FIG. 2

Cyst cavity with its epithelial lining on the right, giant-cell tumour on the left. ×110

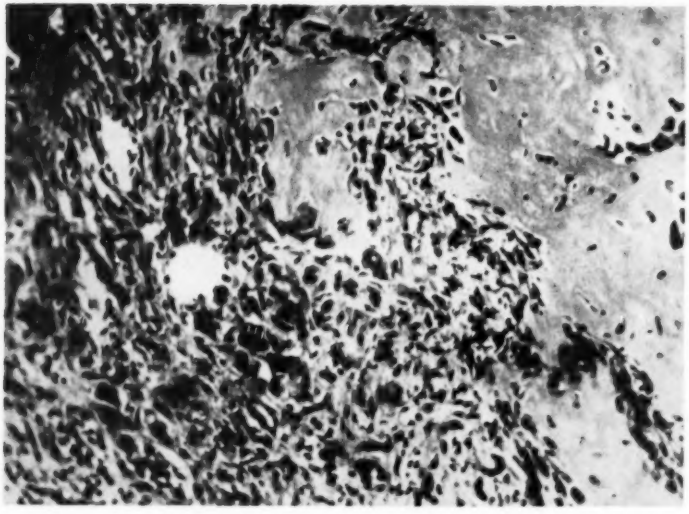

FIG. 3

From a part of the tumour which shows the relationship of the bony plaques to the giant-celled tumour tissue. ×110

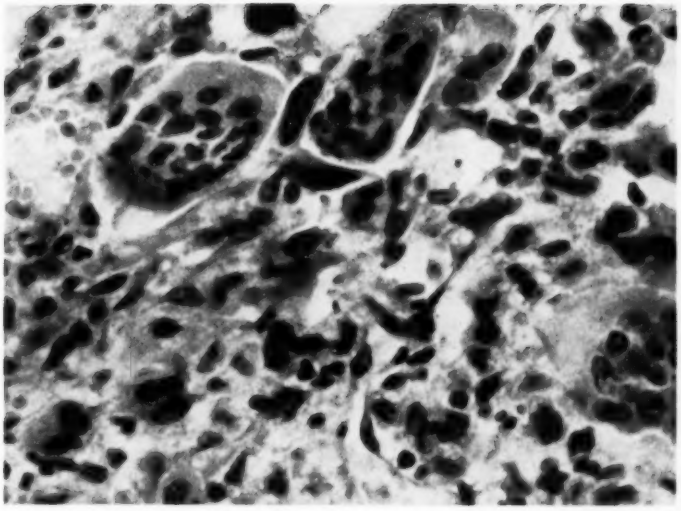

FIG. 4

High power view of the tumour tissue with its giant cells. × 400

tumour. Again there is a wide variation with regard to the proportion that both tumour elements have in the composition of the growth. At the one end of the scale there is a large pseudomucinous cystadenoma with a small solid nodule somewhere in its wall which proves to be a Brenner tumour. At the other end, there is a solid Brenner tumour with a few small cysts lined by the epithelium of the pseudomucinous cystadenoma; and between these two extremes there are many transitory stages. The Brenner tumour shares with the pseudomucinous cystadenoma the uncertainty of histogenesis; also for this tumour there are no normal cells of the ovary from which it could be conveniently derived. It is therefore not surprising that Walthard's cell rests have been claimed as the possible source of origin for both these tumours.

Moreover, besides these two particularly interesting combinations, other neoplasms such as fibromata, myomata, sarcomata, papillomata and carcinomata as well as endometriosis have been discovered in an ovary containing a pseudomucinous cystadenoma and have been regarded as independent growths (for details see Selye, 1946). A pseudomucinous cystadenoma with unusual changes in its stroma which were apparently responsible for a very definite masculinization of the patient was reported earlier by the author in conjunction with Jacobs (Bettinger and Jacobs, 1946).

A combination which to my knowledge has not been seen before occurred recently in our material and seems well worth recording.

The case was that of a young woman, 19 years of age, who had noticed a swelling of her abdomen for a considerable time. At the first examination there was some question about the possibility of a co-existing pregnancy, but the patient solved this problem herself before returning for removal of the ovarian tumour. The tumour was a cystic mass measuring 15 cm. in diameter. It consisted of a few large locules and had in general a thick smooth wall. In several areas there were localized thickenings of the wall and they had on section a honeycomb appearance and contained thick pseudomucin. On one pole there was a solid area, 5×3 cm.; it appeared on the cut surface firm and of brownish colour. Two quite small areas about 1 cm. in diameter, of similar consistency and colour, were seen some distance away on the inner surface of the cystic tumour.

Microscopically, the lining of the main cystic structure consists of tall columnar cells with clear cytoplasm and basal nuclei. They are usually arranged in single, occasionally somewhat folded layers. The "honeycomb" areas consist of small cystic or glandular structures, which are lined by a similar epithelium. Its cells often contain not much mucin and the nuclei tend to fill a greater part of the cell. Although the epithelium is sometimes not as completely differentiated as in the main cavity, there is not sufficient irregularity for a suspicion of malignant change to arise.

The solid brownish tumour has a completely different histological structure. Apart from widespread necrosis and haemorrhage one sees a mixture of young connective tissue, osteoid and osseous tissue. The bony tissues occur in plaques of various sizes; in some parts of the tumour they are quite frequent, in others rather rare. Between bony trabecles there is sometimes loose fibrous tissue of the type seen in bone marrow, but usually osteoid and osseous material is embedded in a young mesenchymal tissue which consists largely of spindly elements. Their nuclei vary considerably in size and shape and so does the amount of cytoplasm surrounding the nucleus. From simple spindle cells to multi-nucleated giant cells all transitional stages can be observed. The giant cells are often indistinguishable from osteoclasts not only with regard to their appearance, but also with regard to their relationship to the bony structures. In short, the general pattern of this tumour is that of a giant cell tumour of bone. The variation in cell form and the rather frequent occurrence of mitoses make it somewhat doubtful whether the tumour can be regarded as entirely benign.

On account of the size of the tumour it was impossible to cut it in serial sections, but in a very large number of representative blocks from all parts of the tumour no other tissue elements were found. The two small brownish nodules described above have also the structure of a giant cell tumour of bone.

An examination of the relationship of the two tumours, the pseudomucinous cystadenoma

and the giant cell tumour, shows them to be distinct histological entities. As the brown tumour forms part of the inner wall of the pseudomucinous cystadenoma, it is covered by columnar epithelium but glandular or cystic structures do not occur within it, nor does the stroma in the cystadenomatous areas contain any of the spindle or giant cells of the brown tumour. In none of the sections was a blending of the two tumour elements seen.

As far as a confessedly incomplete search through the literature indicates, the combination just described has never been recorded. In an attempt at analyzing it, one will have first to assume that the tumour began its development as a teratoma in which differentiation occurred predominantly in one direction only and that then a pseudomucinous cystadenoma resulted. There were, in addition, a few additional foci of differentiation, again in one direction only, i.e., towards bone. In these the development of a giant cell tumour supervened.

Neoplastic change in differentiated tissues of a teratoma (in contrast to the neoplastic behaviour of undifferentiated teratomatous formations) is occasionally seen, most often perhaps in the form of a squamous cell carcinoma arising in epidermal structures of a dermoid cyst. Other tumour formations have been reported, but usually the general pattern of a teratoma is still recognizable. In the present case, however, a sequence of unusual differentiations resulted in the development of two kinds of tissue only, those of a pseudomucinous cystadenoma and of a giant cell tumour of bone.

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THE INTRA-UTERINE GROWTH OF THE FOETAL HEAD AFTER THE 36TH WEEK OF PREGNANCY*

BY

DERK CRICHTON, M.B., D.Phil., M.R.C.O.G.

INTRODUCTION

JOSEPHS (1949) informed a surprised obstetric world that " there is no sign of a growth curve between the 36th and 40th week of pregnancy." The bearing which this statement has on the problem of cephalo-pelvic disproportion cannot be overestimated. Immediate criticism was forthcoming from Moir (1949). He suggested that error arising out of alteration in the position of the head might have given rise to measurements of excessive length in the earlier weeks of pregnancy, whereas later in pregnancy, when the vertex is engaged in the occipito-lateral position, the head would then present a smaller apparent bi-parietal diameter.

Three years later Macdonald (1952) and I (Crichton, 1952) were able to provide proof of continued growth of the foetal head. Macdonald deduced that intra-uterine growth must have occurred in the month before term from his findings that the greater the duration of pregnancy the greater the average length of the bi-parietal diameter of foetal heads. I, on the other hand, reached the same conclusions employing intra-uterine and extra-uterine radiological cephalometry to assess the increase in size of individual foetal heads *in utero* after the 36th week of pregnancy.

Radiological cephalo-pelvimetry is frequently performed before term and appropriate allowance must therefore be made for the subsequent growth of the foetal head in order to appreciate the cephalo-pelvic relationship at term. The work of Scammon and Calkins (1929) is a classic in this field, and their statement that the foetal bi-parietal diameter increases by approximately 0.25 centimetre a week has been widely accepted. Kerr and Moir (1949), however, stated that the rate of growth was 0.2 centimetre a week and Macdonald's (1952) averages give the impression that the rate of growth is about 0.1 centimetre a week.

To me this problem appears to be vitally important. Assume, for the sake of argument, that disproportion is diagnosed radiologically at the 36th week of pregnancy, and that the foetal bi-parietal diameter is 9.0 centimetres. Naturally the obstetrician will be interested to know from the radiologist what will be the cephalo-pelvic relationship at term. Josephs (1949) would state that the foetal head will not grow. Many radiologists, including Reece (1935), would state the bi-parietal diameter will measure 10 centimetres at term, and Kerr and Moir† (1949) would inform us that the bi-parietal measurement will have reached 9.8 centimetres by the 40th week.

In the investigation about to be described I attempted to evaluate these various claims.

THE INVESTIGATION

Moir (1947) was influenced in his opinion by observing the rate of growth of the infant's head in the neo-natal period.

In my own study I have assessed the growth by comparing the intra-uterine and post-natal lengths of (1) the bi-parietal diameter; (2) the occipito-frontal diameter; and (3) the average cranial circumference (that is, the average of two circumferences at 90° relationship to each other).

Post-natal radiological cephalometry was

* Based on work done while holding the post of Dominion Assistant in the Nuffield Department of Obstetrics and Gynaecology, Oxford, in co-operation with the Area Department of Obstetrics and Gynaecology, Oxford.

† Professor Moir has informed me that he has since regarded the rate of growth of the bi-parietal diameter as 0.15 cm. per week.

performed 72 hours after delivery, and only those patients were included in whom the growth interval exceeded 13 days and was less than 6 weeks. The duration of gestation—at the time of the initial radiographic examination—varied from 36 to 44 weeks. Cases were divided into those in which the alteration in measurement had occurred before term, those in which the period of growth included a week or more of gestation both before as well as after the 40th week (the " overlap " group), and those in which the alteration of measurement occurred after term (the " overdue " group).

When considering the growth of the bi-parietal diameter of the foetal head in 43 patients (Table I), only those cases were selected in which the rotation of the skull from the true antero-posterior view did not exceed 20 degrees. An arbitrary deduction of 0.1 centimetre was made from all measurements in the group in which the rotation was judged to lie between 10 and 20 degrees. The reasons for making these necessary corrections were described in brief in a previous communication (Crichton, 1952b).

measurement was assured. Furthermore an example is provided in the appended photograph (Fig. 1) which illustrates how it is possible for a bi-parietal diameter to measure 10.0 centimetres at the 36th week of pregnancy (suggesting that the baby already weighs over 9 pounds), and yet to have decreased to 9.5 centimetres by the 40th week, when the baby was born weighing 6 pounds 11 ounces. Note that the apparent bi-parietal diameter was suitably placed for accurate measurement and that the head was centrally placed. Consequently the criteria for cephalometry of optimum precision were satisfied. The average circumference reading, on the other hand, showed that the head was small at the 36th week. Thus it was possible to avoid making a gross error in cephalometric prognosis, because reliance was not put on measurement of any one single diameter—a possible source of serious error, as I have shown in a previous communication (1952b).

TABLE I

The intra-uterine growth in centimetres of the bi-parietal diameter after the 36th week of pregnancy (43 *cases*).

Growth per week	37–40 weeks	37–44 weeks " overlap " group	41–44 weeks " overdue " group
Increase of 0.25 cm.	1 case	–	–
" " 0.20 "	–	1 case	–
" " 0.15 "	4 cases	2 cases	1 case
" " 0.10 "	10 cases	5 cases	4 cases
" " 0.05 "	2 cases	4 cases	2 cases
No growth	1 case	2 cases	1 case
Decrease of 0.05 "	–	–	1 case
" " 0.10 "	1 case	1 case	–
	19 cases	15 cases	9 cases

DISCUSSION

It will be noted that the rate of growth of the cranial measurements is not uniform, and the obvious question which suggests itself is: " are these irregularities not due to errors in cephalometry? " Small errors may rest in the cephalometry technique but great care has been taken to include only those cases in which accurate

This case also supports a belief that has been forced on me, namely that minimum growth, or even arrest of growth, of the head may occur in the path of greatest resistance. For instance, in this case both the average circumference and the occipito-frontal diameter increased in length; but the bi-parietal diameter became smaller. To continue this diversion from the main topic, I should like to state my belief that a particular diameter, which grows abnormally slowly or not at all, will be correspondingly less mouldable in labour.

It can thus be firmly stated that, contrary to the findings of Josephs (1949), the head does increase in size in the last 4 weeks of gestation. This is shown in an increase of the bi-parietal diameter in the great majority of cases, and in an increased average circumference in all save one doubtful case.

The average growth of the bi-parietal diameter will be noted to lie in the neighbourhood of 1 to 1.2 millimetres—about half the figure suggested by Kerr and Moir (1949) and Scammon and Calkins (1929).

There can be little doubt that Joseph's error lay in attempting (without suitable compensation) to measure the bi-parietal diameter in heads which tended to be high and oblique between the 35th to 37th weeks of pregnancy.

The rate of growth of the occipito-frontal diameter (Table II) is probably in the region of 0.12 centimetre per week. The average circumference of the foetal head usually increases by 0.3 centimetre per week.

But what of those patients in whom pregnancy continues after the expected date of delivery? The problem becomes all the more acute in patients in whom disproportion is already present, and it is regrettable that it is precisely in these patients that "post-maturity" is liable to occur. I should like to be able to state that the growth of the head after term is negligible, and in so doing I would be voicing the opinion of the majority. But such is far

TABLE II

The intra-uterine growth in centimetres of the occipito-frontal diameter of the skull after the 36th week of pregnancy (49 *cases*)

Growth per week	37–40 weeks	37–44 weeks "overlap" group	41–44 weeks "overdue" group
Increase of 0.25 cm.	5 cases	–	–
,, ,, 0.20 ,,	3 cases	5 cases	2 cases
,, ,, 0.15 ,,	5 cases	5 cases	3 cases
,, ,, 0.10 ,,	4 cases	6 cases	3 cases
,, ,, 0.05 ,,	–	1 case	–
No growth	1 case	2 cases	1 case
Decrease of 0.10 ,,	1 case	2 cases	–
	19 cases	21 cases	9 cases

TABLE III

The intra-uterine growth in centimetres of the average cranial circumference after the 36th week of pregnancy* (68 *cases*)

Growth per week	37–40 weeks	37–44 weeks "overlap" group	41–44 weeks "overdue" group
Increase of 0.60 cm.	1 case	1 case	–
,, ,, 0.50 ,,	3 cases	1 case	1 case
,, ,, 0.40 ,,	10 cases	5 cases	2 cases
,, ,, 0.30 ,,	8 cases	10 cases	4 cases
,, ,, 0.20 ,,	7 cases	4 cases	4 cases
,, ,, 0.10 ,,	2 cases	1 case	1 case
No growth	–	1 case	–
Decrease of 0.10 cm.	–	1 case	–
,, ,, 0.50 ,, †	–	1 case	–
	31 cases	25 cases	12 cases

* Average of two circumferences at 90° relationship.

†This incongrous reading was probable caused by an error arising out of upward movement and rotation of the foetal head in the interval between the two radiographic examinations.

from the truth, for reference to Tables I, II, and III shows that the bi-parietal and the occipito-frontal diameter, as well as the average circumference of the skull, continue to increase in size at a rate which almost parallels that obtaining before term.

If a patient is allowed to go a fortnight past her estimated date of delivery one may rest assured that the area in the plane of the same presenting diameter will have increased by about 4 per cent. Couple with this the reduction in mouldability, and one might assume that these were all-powerful indications to induce labour in all patients with cephalo-pelvic disproportion at term. But what of the resultant uterine action? If we believe that uterine action is markedly inferior after labour has been induced at term by comparison with the strength of uterine action following the spontaneous onset of labour in the overdue period, then we have every right to leave the decision to Nature. Per contra, were we to hold the opinion that the uterine action which results after either course of action is approximately the same, then we should tend to induce labour. This problem is complex and there remains much scope for individual impressions. But this at least is clear from my studies: the foetal head continues to increase in size in the weeks following term.

Summary and Conclusions

(1) The bi-parietal diameter, the occipito-frontal diameter, and the average cranial circumference were measured *in utero* in 68 patients after the 36th week of pregnancy. Those babies delivered not less than a fortnight later were subjected to radiological cephalometry 72 hours after birth. Only those cases were included in which measurement of the bi-parietal diameter was known to be free from error.

(2) The rate of growth varies slightly from case to case, and there is variability of the rate of growth of different diameters in the same skull. I believe that this is because the rate of growth of the skull in a particular direction is to some extent governed by the resistance encountered in that direction. Growth may even cease in that particular direction, but compensatory increase occurs elsewhere. It is even possible for the bi-parietal diameter to decrease in size after the 36th week of pregnancy.

(3) Those diameters which fail to grow, or grow abnormally slowly, are less capable of moulding in labour.

(4) After the 36th week of pregnancy the rate of growth of the bi-parietal diameter is about 0.1 to 0.12 centimetre per week. The occipito-frontal diameter increases at the rate of 0.11 centimetre per week, and the average cranial circumference enlarges by 0.3 centimetre per week.

(5) Growth continues, but the rate is lessened to a minor extent after the 40th week of gestation.

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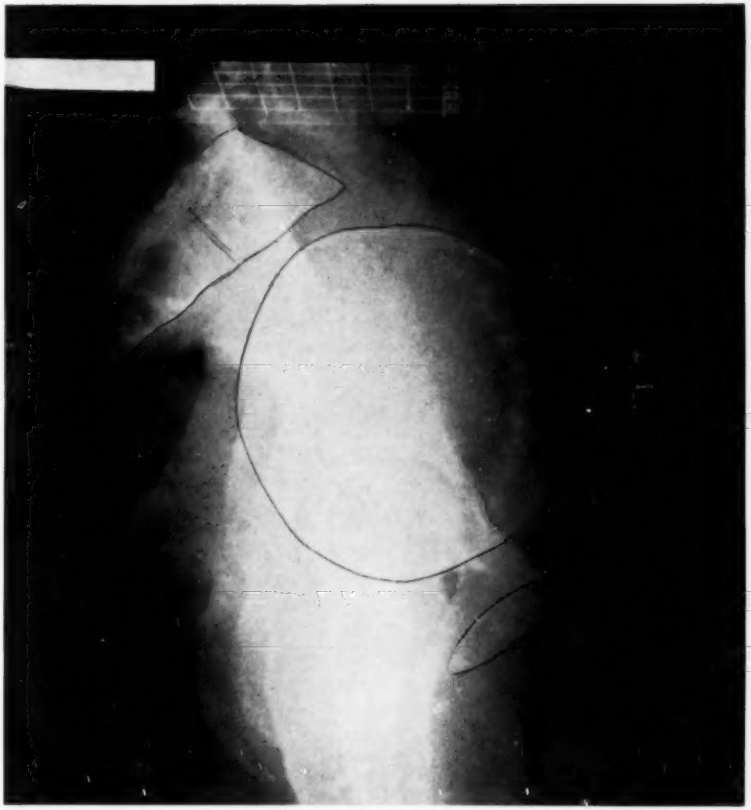

FIG. 1

The bi-parietal diameter measured 10.0 centimetres at the 36th week of pregnancy, and the abnormally broad shape of the head is obvious.
A normal delivery occurred at the 40th week, and the bi-parietal diameter of the 6 pounds 11 ounces baby (measured 72 hours after delivery) was 9.5 centimetres. The average cranial circumference had increased in size from 30.8 centimetres at the 36th week to 31.9 centimetres at term.

D.C.

VAGINAL DELIVERY AFTER CAESAREAN SECTION*

BY

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IN the last 20 years it has been confidently claimed on many occasions that the old dictum "once a Caesarean, always a Caesarean" was no longer true. It is, therefore, disconcerting to read Greenhill's statement (1949): "I now almost routinely perform a Caesarean section on all women who previously have had a Caesarean section, regardless of the indication for the first operation." It is perhaps even more disturbing to find that similar views are expressed by obstetricians in England. Theobald (1949), for example, says in referring to a group of 20 to 30 women delivered *per vias naturales* after previously being subjected to Caesarean section: "we have recently been impressed with the dangers of this line of treatment and in consequence the number of repeat sections is likely to increase during the next few years." These challenging statements provoked me to make a retrospective investigation into the obstetric history of all patients delivered in the Maternity Hospital at Leeds after Caesarean section. The investigation covers the years 1926 to 1948 inclusive, and includes all patients previously subjected to Caesarean section, irrespective of whether the operation had been performed in the hospital or elsewhere.

The obstetric management of the previously sectioned patient has been discussed frequently in recent years (Kuder and Dotter, 1944; Duckering, 1946; Hindman, 1948; Iturriaga, 1949; Schnitz and Baba, 1949; Browne, 1951; Cosgrove, 1951; Hayes, 1951; and Schnitz and Gajewski, 1951).

Most writers are in general agreement that there are two fundamental questions to be answered before deciding whether or not repeat operation should be adopted as the standard method of delivery for patients previously subjected to Caesarean section. The two questions are: (1) Is the frequency of rupture of the uterine scar so great as to make vaginal delivery unjustifiably risky?; (2) What results may be expected if previously-sectioned patients are allowed to go into labour?

The results of this investigation are summarized in Table I, and this material has been analyzed to find an answer to the two questions posed above.

* Read at a Meeting of the North of England Obstetrical and Gynaecological Society, held in Newcastle on Friday, 6th June, 1952 (see page 266).

TABLE I

	Classical section	Lower segment section	Total
Number of primary sections	806	1161	1967
Number who subsequently conceived	286	353	639
Number of subsequent pregnancies	427	472	899
Result of subsequent pregnancies:			
Abortion	27	23	50
Repeat Caesarean sections: (*a*) Not in labour	222	139	361
(*b*) In labour ...	104	189	293
Vaginal delivery	74	121	195
Number of cases of ruptured scar	4	2	6

(1) *Is the frequency of rupture of the uterine scar so great as to make vaginal delivery unjustifiably risky?*

(*a*) *Rupture of the classical scar.* There were 4 cases of rupture of the scar after classical section among 286 patients who had a total of 427 pregnancies after primary section. Of this total, 27 pregnancies ended spontaneously before the 28th week; of the remaining 400, 222 were terminated by repeat section before the onset of labour, and 104 by repeat section after at least 3 hours of active labour. The remaining 74 were delivered vaginally.

The 4 cases of rupture all occurred after the onset of labour; the incidence of rupture is therefore 1 per cent of all mature pregnancies, and 2.2 per cent of all cases subjected to a minimum of 3 hours of active labour. All 4 mothers and 2 of the babies survived.

(*b*) *Rupture of the lower segment scar.* There were 2 cases of rupture of the scar after lower segment section, using a transverse incision in the uterus, among a total of 353 patients who had a total of 472 pregnancies. Of this total, 23 ended spontaneously before the 28th week. Of the remaining 449 cases, 139 were delivered by repeat section before the onset of labour, 189 by repeat section after a minimum of 3 hours in labour. The remaining 121 were delivered vaginally.

Both cases of rupture of the scar (previously reported by Lawrence, 1949) occurred after the onset of labour at term; the incidence of rupture is therefore 0.47 per cent of mature pregnancies, and 0.65 per cent of cases subjected to a minimum of 3 hours of active labour. Both mothers and both babies survived.

There were thus 6 cases of rupture in the whole series. None occurred before the onset of labour, and with the marked decline in the use of the classical incision such an occurrence is likely in future to be extremely rare. Rupture of the uterine scar in labour occurred more than 3 times as often after the classical as after the lower segment operation. The occurrence of 2 ruptures among 310 lower segment scars (all transverse) during subsequent labour is a reminder that even a lower segment scar is a potential danger, not sufficient to preclude subsequent labour, but great enough to demand that such labour be managed in hospital under expert supervision.

(2) *What results may be expected if previously-sectioned patients are allowed to go into labour?*

The main points for consideration under this heading are: (*a*) In what proportion of the cases was vaginal delivery achieved? (*b*) In what proportion was assistance required? (*c*) What was the duration of labour? (*d*) Is the risk to the foetus materially increased?

(*a*) *In what proportion of the cases was vaginal delivery achieved?* After classical section 18.5 per cent (74 out of 400) were delivered vaginally, and after lower segment section 26.9 per cent (121 out of 449), with a mean of 22.9 per cent (195 out of 849).

It is certain that these are minimum values. The investigation covers a long period, during the early part of which labour after Caesarean section was regarded as risky, and repeat section resorted to at the first suggestion of delay. Only in the latter part of the period under review, when lower segment operations predominated, did a more courageous attitude result in a more thorough trial and a greater proportion of vaginal deliveries.

When the figures were examined with regard to the indication for the original section, the results shown in Table II were obtained. This table shows that where the original indication can be regarded as persisting (e.g., contracted pelvis and disproportion) the proportion of vaginal deliveries is small, while in those cases in which the original indication is non-recurrent (e.g., antepartum haemorrhage) the proportion of vaginal deliveries is high. This result may be artificial in that, where it is known that section has previously been considered necessary on account of a persisting indication, repeat section is readily resorted to, without adequate trial of labour, whereas a more prolonged test, with a higher proportion of successes, is allowed where the indication is non-recurrent.

(*b*) *In what proportion was assistance required?* Assistance was required to complete 24 of the total of 195 vaginal deliveries. The detailed analysis is given in Table III, which shows that assistance was required on account

TABLE II

Indication	Subsequent pregnancies	Abortion	Repeat C.S.		Vaginal delivery	
			Not in labour	In labour	Number	Percentage
Disproportion	644	29	294	242	79	11.2
Antepartum haemorrhage	68	6	11	10	41	66.1
Distress	34	3	8	11	12	38.7
History	36	2	17	8	9	26.5
Heart disease	1	–	1	–	–	–
Toxaemia	16	2	4	3	7	50.0
Inertia	66	4	18	15	29	46.7
Prolapsed cord	20	–	5	2	13	65.0
Miscellaneous	14	4	3	2	5	50.0
Total	899	50	361	293	195	

TABLE III
Indications for assisted delivery

	Distress		Inertia	Delay in second stage	P.O.P. and D.T.A.	Not stated	Total
	Maternal	Foetal					
(1) Classical section:							
(*a*) No previous vaginal delivery	1	1	1	–	3	1	7
(*b*) Previous vaginal delivery	–	1	–	–	–	–	1
(2) Lower segment section:							
(*a*) No previous vaginal delivery	1	2	1	3	4	3	14
(*b*) Previous vaginal delivery	–	–	1	1	–	–	2
Total	2	4	3	4	7	4	24

P.O.P.=Persistent occipito-posterior. D.T.A.=Deep transverse arrest.

of maternal distress in 2 cases, foetal distress in 4 cases, inertia in 3 cases, delay in second stage 4 cases, persistent occipito-posterior position and deep transverse arrest in 7 cases, and for unspecified reasons in 4 cases. With the exception of the 4 cases for which no reason is given, an acceptable obstetrical reason was given, and it has obviously not been the practice to apply forceps as a prophylactic measure.

Table IV shows that assistance was required for 2 cases within 9 hours of the onset of labour, 1 between 9 and 12 hours, 10 between 12 and 24 hours, 9 between 24 and 48 hours, and 2 after 48 hours of labour, i.e., of 112 patients delivered vaginally after labour of 24 hours or less only 13 required assistance. This again shows that there was no planned resort to the forceps at full dilatation of the cervix, but that where labour was progressing normally no interference was considered necessary.

(*c*) *What was the duration of labour?* The duration of the first labour after Caesarean section is shown in Table IV, and ranged from 2 to 49 hours. There is a striking similarity in the average duration of labour in the two main groups. Those who had had a previous vaginal delivery averaged 14 hours in the classical group and 13 hours in the lower segment group. Corresponding figures for the patient who had had no previous vaginal delivery were 20 hours and 19 hours. In the matter of duration, therefore, the type of previous section does not seem to have any important influence.

Where there has been no vaginal delivery previously the length of labour approximates to that of labour in a primigravida, and where there has been a previous vaginal delivery it approximates to that of labour in a multigravida.

Where there had been no previous vaginal delivery 71 per cent of the classical group and

75 per cent of the lower segment group were delivered within 24 hours in the first labour after section (Table V). Where there had been a previous vaginal delivery the corresponding figures were 89 per cent and 96 per cent. In only a small proportion, therefore, did labour exceed the usually accepted limits of normal. In subsequent labours the average duration was slightly reduced in 3 of the 4 groups, though here the small number of cases makes the figures unreliable (Table VI).

(*d*) *Is the risk to the foetus materially increased?* Maturity at delivery is shown in Table VII. Twelve out of 195 infants were delivered before the 36th week of pregnancy, and 28 were delivered after the 40th week, but the great majority were delivered between the 36th and 40th weeks, and there does not seem to be any markedly increased risk of premature labour. Not only were the infants mature, but average weight at birth was as great as that of the babies delivered by Caesarean section in 3 out of 4 groups (Table VIII).

There were 19 stillbirths, giving an incidence of 10 per cent (Table IX). In 7 cases death occurred *in utero* before the onset of labour, and no adequate explanation is offered. In 3 cases the death of the foetus was attributed to disease in the mother, and in 1 case to congenital abnormality of the foetus. One premature baby was born dead before the mother reached hospital. There remain, however, 5 cases in which death was attributed to birth trauma, and it seems that in these cases the obstetric manage-

TABLE IV

Duration (in hours) of first labour after Caesarean section

	0–3	3–6	6–9	9–12	12–24	24–48	Over 48	Range	Mean
(1) Classical section:									
(*a*) No previous vaginal delivery	0	2	2(1)	4	12(3)	6(2)	2(1)	5–49	20
(*b*) Previous vaginal delivery	2	2	3	4	5(1)	2	0	2–32	14
(2) Lower segment section:									
(*a*) No previous vaginal delivery	0	7	8(1)	11(1)	29(5)	17(6)	1(1)	4–57	19
(*b*) Previous vaginal delivery	1	6	2	0	12(1)	1(1)	0	2–27	13

The figures in parentheses show the numbers of assisted deliveries, i.e., forceps or breech extraction.

TABLE V

	Number delivered within 24 hours	Percentage
(1) Classical section:		
(*a*) No previous vaginal delivery	20	71
(*b*) Previous vaginal delivery	16	89
(2) Lower segment section:		
(*a*) No previous vaginal delivery	55	75
(*b*) Previous vaginal delivery	21	96

TABLE VI

Duration (in hours) of labour after Caesarean section

	First labour	Labour other than first	All labours
(1) Classical section:			
(*a*) No previous vaginal delivery	20	7	18
(*b*) Previous vaginal delivery	14	9	13
(2) Lower segment section:			
(*a*) No previous vaginal delivery	19	11	17
(*b*) Previous vaginal delivery	13	15	13

TABLE VII

Maturity at delivery

	28–30	30–34	34–36	36–40	Over 40	Twins	Stillbirths
(1) Classical section:							
(*a*) No previous vaginal delivery ...	–	1	–	26	5	2	4
(*b*) Previous vaginal delivery	–	1	1	21	2	–	4
(2) Lower segment section:							
(*a*) No previous vaginal delivery ...	1	6	–	71	16	2	9
(*b*) Previous vaginal delivery	–	–	2	19	5	1	2
Total	1	8	3	137	28	5	19

TABLE VIII

Birth weight

	Caesarean section			Subsequent vaginal delivery		
(1) Classical section:	pounds	ounces	(g.)	pounds	ounces	(g.)
(*a*) No previous vaginal delivery	6	7	(2,922)	7	1	(3,206)
(*b*) Previous vaginal delivery	6	5	(2,866)	6	10	(3,007)
(2) Lower segment section:						
(*a*) No previous vaginal delivery	7	6	(3,348)	7	3	(3,263)
(*b*) Previous vaginal delivery	7	6	(3,348)	7	6	(3,348)

TABLE IX

Stillbirths

19 cases in 195 deliveries (10 per cent)	
Intra-uterine death	7
Birth trauma:	
Forceps (contracted outlet)	1
Breech	3
Craniotomy	1
Prolapsed cord	2
Maternal disease:	
Pneumonia	1
Nephritis	1
Toxaemia	1
Hydrocephaly	1
B.B.A. (premature)	1

ment was at fault, and repeat section would have been preferable. In the 2 cases of prolapse of the cord repeat section might also have been preferable, though if pulsation of the cord had already ceased the repeat operation would have had no advantage.

There are thus 7 cases in which better results might have been expected from repeat section, and in this respect vaginal delivery must be considered as carrying an increased risk to the baby. Had repeat section been performed with delivery of a live child in these cases the stillbirth rate for the cases delivered vaginally would have been 6.3 per cent (12 in 188 cases), which compares fairly well with most hospital statistics.

DISCUSSION

The story would be incomplete without mention of the results of repeat section. In 654 instances pregnancy was terminated by repeat section, 361 (56 per cent) being performed before the onset of labour or within 3 hours. There were 9 stillbirths, an incidence of 2.2 per cent. The average birth weight of the babies born by primary and repeat section differed only by an insignificant amount (Table X).

These results are obviously good, but it is clear that in the majority of cases equally good results could have been obtained had the patients been allowed a fair opportunity to test their capabilities in labour. The high proportion of elective sections before or early in labour indicates the prevailing bias: 48 per cent of the primary sections were performed for contracted pelvis or disproportion, but 86 per cent (562 out of 654) of the repeat operations were performed for this indication (Table XI). There

TABLE X

Birth weight (repeat section)

	First section			Repeat section		
	pounds	ounces	(g.)	pounds	ounces	(g.)
Classical section	6	13¼	(3,107)	7	0	(3,178)
Lower segment section	7	5¼	(3,327)	7	4¼	(3,298)

TABLE XI

Indication for repeat section

Indication for primary section	Disproportion	Antepartum haemorrhage	Distress	History	Heart	Toxaemia	Inertia	Prolapsed cord	Miscellaneous
Disproportion	501	6	4	11	1	–	4	–	12
Antepartum haemorrhage ..	10	2	1	3	1	1	–	–	1
Distress	13	1	2	2	1	–	3	–	–
History	9	–	2	8	–	1	–	–	2
Heart	2	–	–	–	–	–	–	–	–
Toxaemia	4	–	–	–	–	–	1	–	–
Inertia	21	–	4	4	–	–	6	1	–
Prolapsed cord	4	–	–	2	–	–	–	–	–
Miscellaneous	–	–	–	1	–	–	1	–	3
Total	562	9	13	31	3	2	15	1	18

was obviously a very great readiness to perform repeat section on cases previously operated on for this condition, and a very slight inclination to allow a trial of labour. That good results can be obtained by trial labour after section for contracted pelvis has been shown by Herd (1949) who reported 43 per cent of vaginal deliveries after section for disproportion without foetal loss. His cases were personally observed and carefully scrutinized, and were collected over a short period. My cases extended over a much longer period and were, therefore, subjected to the changing trends of obstetric thought, from the early days of " always a Caesarean " to the present time when the possibilities of vaginal delivery are more fully appreciated.

This account is entirely retrospective, and refers to patients who may almost be said to have achieved vaginal delivery in spite of the obstetrician, since repeat section before or at the start of labour has been the method of choice in so great a proportion of the cases. It would be interesting to compare these figures with those obtained as a result of a strictly conservative attitude to repeat Caesarean section, and a deliberate policy of allowing labour to end naturally wherever possible.

My thanks are offered to the past and present consultants of the Maternity Hospital at Leeds for allowing me access to their case records.

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THE COMPOSITION OF LIQUOR AMNII IN HAEMOLYTIC DISEASE OF THE NEWBORN

BY

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As serological data are of little value in predicting the state of a foetus to be delivered of a sensitized Rhesus-negative woman, an investigation was undertaken to test the value of analysis of the liquor amnii during the antenatal period. A preliminary survey (Bevis, 1950) showed that this might be of value if specimens were obtained from the 22nd week of pregnancy onwards. It is usually impossible to obtain specimens before this time, but afterwards specimens can be taken fairly easily at fortnightly intervals, about 10 ml. being removed. It is stressed that, to the best of my knowledge, abdominal paracentesis produces no ill effects on the mother or foetus apart from slight abdominal discomfort lasting about 6 hours. No case of stillbirth or premature labour can be ascribed to the procedure and there have been no skin lesions produced in the foetuses.

Surprisingly little is known about the composition of normal liquor and so a large number of specimens have been examined to discover average values for some of the constituents. The results indicate that the composition of liquor varies considerably, but help in prognosis for the foetus is obtained from the concentrations of non-haematin iron and urobilinogen. The iron concentration is related to the degree of foetal anaemia and the urobilinogen to the development of kernicterus.

RESULTS

A total of 205 specimens have been examined, taken from 98 patients of whom 41 gave birth to infants suffering from haemolytic disease of the newborn. As many tests as possible were carried out on each specimen and details are given in an appendix to this paper. For convenience the constituents are considered in alphabetical order.

Bilirubin. In no specimen has a direct van den Bergh reaction been obtained, even in the presence of meconium. The amount present is variable, ranging from 0 to 7.5 mg./100 ml. No correlation has been found between the concentration and the severity of the disease in the foetus, but, as may be expected, the concentration is increased when meconium is present. The relationship between the icteric index of the liquor and the concentration of bilirubin is discussed later.

Biliverdin. Whenever bilirubin is present a variable amount of biliverdin is found but the amount is small in the absence of meconium, ranging from 0 to 1 mg./100 ml. (meconium absent).

Chlorides. The concentration varies between different patients and in the same patient at different times.

Mean values at or near term are: NaCl, 508 ± 123 mg./100 ml.; Cl, 87 ± 21 mEq./L. No trends in the concentration were observed.

Cholesterol. The concentration is very variable, ranging from 8.1 to 58.6 mg./100 ml. The concentration is related to the amount of vernix present but the relationship is not absolute. No other trends were discovered.

Copper. The concentration varies widely, ranging from 1.4 to 120 μg./100 ml. No trends were observed and the amount present is not related to the iron concentration.

Coproporphyrin. The concentration in liquor from normal foetuses is fairly constant compared with other constituents, the mean being 32.7 ± 17.7 μg./100 ml. With increasing severity of the haemolytic process the concentration is increased, the highest value recorded being 220 μg./100 ml. Too few estimations have been performed on affected babies to draw definite

conclusions, but increased concentration does not appear to be related to the incidence of kernicterus.

Isomer analysis indicates that in normal liquor no coproporphyrin I is present and in the case referred to, in which the total concentration reached 220 μg/100 ml., most of the increase was due to the I isomer although a trace of the III isomer was present.

Icteric Index. Although yellow coloration of the liquor and vernix indicates a grave prognosis for the infant, assessment of the icteric index of the liquor shows that even in normal liquor there is some yellow tinting, the range being 0.2 to 1.5 units. No correlation can be shown between the bilirubin content of the liquor and its colour (Fig. 1). No carotinoids have been found in liquor but a brown substance has been isolated which has the properties ascribed by Rimington and Stewart (1932) to lanaurin or mesobilifuscin. There are as yet no methods for measuring the concentration of this substance but it appears that all the yellow colour in bilirubin free liquor is due to this substance. The occurrence of appreciable quantities of this substance is always associated with the development of kernicterus (Fig. 2), but, as its occurrence is linked with the concentration of urobilinogen in the liquor, further discussion is deferred.

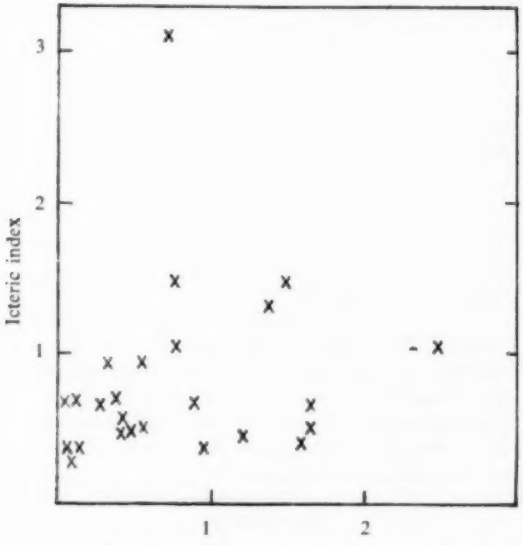

FIG. 1
Relationship between the colour of the liquor and its bilirubin content.

Iron. The total iron content of the liquor is difficult to assess, as the slightest contamination with haemoglobin masks all variation. The concentration of non-haematin iron (the equivalent of serum iron) is remarkably constant in normal liquor, the mean being 26.7 $\pm$ 10.4 μg./100 ml. The concentration increases as the foetus is affected with haemolytic disease of the newborn and the relationship (Fig. 3), although in the form of a sigmoid curve, can be accurately reproduced from 9 to 18 g./100 ml. haemoglobin by the logarithmic function: haemoglobin = 28.8 – 8.4 log iron (μg./100 ml.) where the haemoglobin concentration is expressed in grams per 100 ml. cord blood and the iron in micrograms per 100 ml. liquor. This enables a standard curve to be constructed and used to predict the severity of the haemolytic anaemia. The saturation of the liquor for iron has been estimated and it is found that the liquor is always fully saturated whatever the concentration of iron found. This implies that the protein which binds the iron is produced in the liquor at the same rate as the iron; it is probable, therefore, that the iron is excreted into the liquor by the foetus.

Protein. The composition of the protein fraction of the liquor is obscure, but besides albumin and globulin there is a moderate amount of mucoprotein present Attempts to identify this mucoprotein have been unsuccessful and so quantitative differentiation has not been attempted. The total concentration varies considerably, the mean being 446 $\pm$ 144 mg./100 ml.; 1.08 $\pm$ 0.35 mEq./L. No trends were observed in the differing concentrations.

Sugars. The concentration of *glucose* varied considerably, the mean being 26.4 $\pm$ 8.1 mg./100 ml. No trends were discerned. The concentration of *laevulose* also varied, the range being 0 to 11 mg./100 ml. In some patients it disappeared from the liquor in which it had been present and reappeared later in pregnancy. No explanation could be found for this and no specific trends in the concentration were

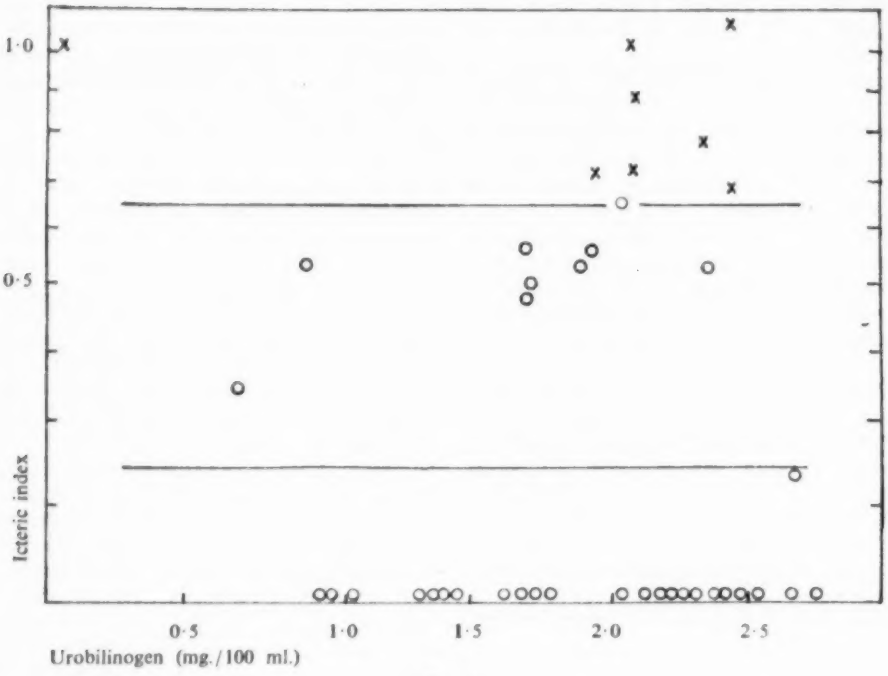

FIG. 2

Relationship between the icteric index of the liquor (minus the contribution of bilirubin) and the development of kernicterus. The icteric index is plotted on a logarithmic scale and the horizontal lines are the mean and the upper limit of normal calculated from the unaffected infants.

0=normal x=kernicterus.

observed. The amount of *pentoses* showed wide variation, ranging from 2.0 to 5.7 mg./100 ml. No phosphorylated pentose could be found and, apart from a rise in the total pentose concentration in pre-eclampsia, no trends were observed.

Urea. The concentration in normal pregnancy shows a progressive rise as pregnancy progresses, the range being 12.7 to 37.1 mg./100 ml. No other trends were observed.

Urobilinogen. The concentration in normal pregnancy rises slowly to a fairly constant maximum shortly before term, the mean being 1.79 ± 0.32 mg./100 ml. The concentration falls sharply as kernicterus develops (Bevis, 1952), but tends to rise afterwards. This drop in concentration is a reliable guide to the development of kernicterus and is linked with the icteric index and the concentration of mesobilifuscin. This relationship is discussed later.

The concentration of urobilinogen IXa (mesobilene-b) has been studied, but only traces have been found. Its concentration does not appear to be related to the amount of urobilinogen (tetrahydromesobilene-b) present. It has not been possible to determine the optical rotation of the urobilinogen present.

DISCUSSION

The composition of the liquor amnii varies considerably in different patients and in the same patient at different times. Comparison with the results of other workers (Table I) shows only minor differences. In general it may be said

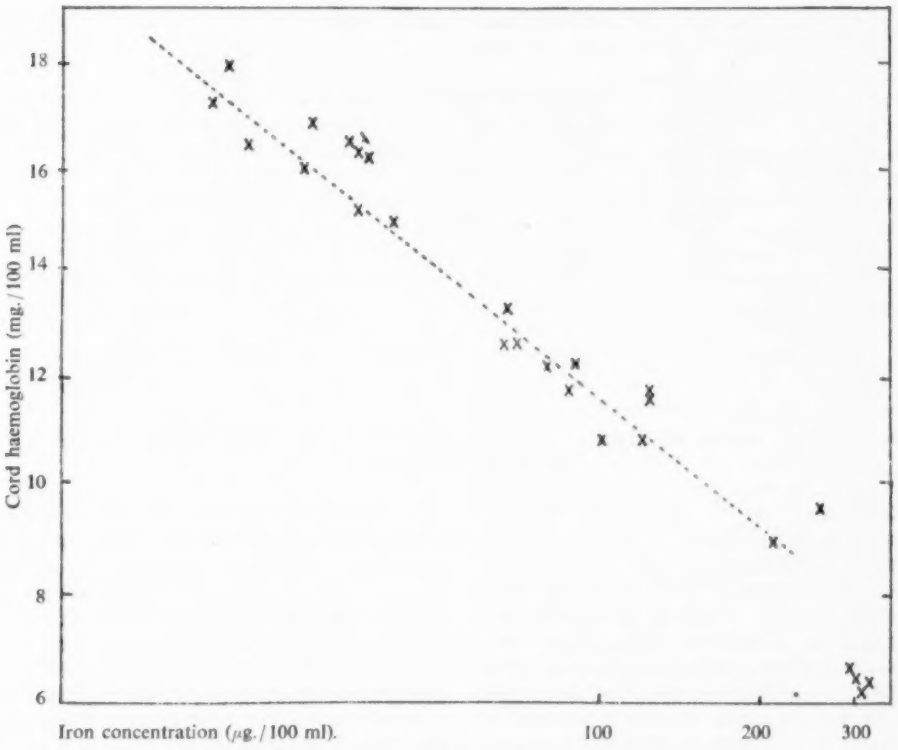

FIG. 3

Relationship between the nonhaematin iron of the liquor and the cord haemoglobin of the foetus. Iron concentrations are plotted on a logarithmic scale and the dotted line is the calculated regression line.

that liquor is a fluid with characteristics between blood and cerebrospinal fluid.

It is now known that the liquor amnii is not a static fluid, but that its water content is changed hourly (Gellhorn and Flexner, 1942), although other constituents remain for a longer time. Also, since iron reaches the liquor within 40 minutes of oral administration to the mother (Pommerenke *et al.*, 1942), it is likely that the liquor is a secretion and not a dialysate, a finding further confirmed by Rosa (1951). The amount of the contribution of foetal urine to the total volume is only of academic interest in view of the speed of these changes and, although the present work confirms the findings of Guthmann and May (1932) that the concentration of urea increases as pregnancy advances, this is probably due merely to the increased size of the foetus.

It is probable that liquor is an active secretion of the placenta and possibly of the amnion (Kropp, 1940; Rosa, 1951), but it is also evident that excretion products of the foetus pass into it, probably from the skin and possibly also from the lungs.

The constituents of the liquor fall into two main groups, those arising from the metabolism of haemoglobin and the remainder. Of the general constituents little need be said. The variable presence of laevulose is interesting, but

TABLE I

Composition of Liquor Amnii

	Shrewsbury (1933)	Tankard *et al.* (1934)	Makepeace *et al.* (1931)	Cantarow *et al.* (1933)	Uranga Imaz and Gascon (1950)	Bevis (1952)
Chloride	540–670	660	622	–	350	508
Glucose	0–91	–	33	0–59	40	27
Protein	25–600	350	233	530	210	446
Cholesterol	nil	–	–	–	19	8–58
Urea	10–73	109	–	–	30	12–37
Bile pigments	nil	–	–	–	–	0–2.5
Icteric index	–	–	–	–	–	0.2–7
Urobilinogen	–	–	–	–	–	1.79
Laevulose	–	–	–	–	–	0–11
Iron	–	–	–	–	–	26 (μg.)
Copper	–	–	–	–	–	1.4–120 (μg.)

All values are mg./100 ml. except where otherwise stated and refer to mean values at term except where the range is given.

no conclusions can be drawn; the increased amount of pentose in pre-eclampsia may indicate a relative ischaemia of the uterus and confirms the work of Green *et al.* (1951), and is possibly additional evidence in favour of the theory of Bastiaanse and Mastboom (1950) of the aetiology of pre-eclampsia. The main interest of the investigation has been in the breakdown products of haemoglobin. The concentration of non-haematin iron in the liquor is related to the severity of the haemolytic anaemia of the foetus (Fig. 3). This relationship is expressed by a sigmoid curve, but a reasonable fit is obtained between 9 and 18 grams of haemoglobin per 100 ml. cord blood by the line: cord haemoglobin = 28.4 – 8.4 log iron (μg./100 ml.). As these limits cover the majority of infants, the equation is useful for plotting a standard curve. The limiting concentration is about 320 μg. per 100 ml. liquor as at this concentration the foetus dies and labour rapidly follows. This rapid onset of labour implies that there is some irritation of the uterus. Concentrations of iron below this limit give a sound idea of the severity of the haemolytic anaemia, but in severely affected infants the concentration of iron varies after a critical level has been reached, and it is therefore essential to record the highest concentration attained. The relationship between changes in iron concentration and the duration of the pregnancy are also important. The foetus is sometimes severely affected by the 32nd week and in these cases the outlook is practically hopeless. In some cases, however, the changes are not seen until shortly before term and it is suggested that there is a definite place for the premature induction of labour in these cases in spite of the general findings of Mollison and Walker (1952).

It was hoped that the behaviour of copper in the liquor would explain something of the changes in the iron concentrations or of the incidence of kernicterus (in view of its general resemblance to Wilson's disease). This has not been found and there is no apparent relationship between iron and copper in the liquor.

The presence of bile pigments in the liquor is of great importance in foretelling the development of kernicterus. Bilirubin is usually and urobilinogen is always present in the liquor. In view of the doubts concerning the origin of the urobilinogen in the liquor and its peculiar behaviour in haemolytic disease of the newborn, care has been taken to confirm that the substance estimated really was urobilinogen (tetrahydromesobilene-b). Winternitz (1926) showed that urobilin reached the foetus from the maternal circulation, but in view of the drop in concentration that occurs in kernicterus it is improbable that much reaches the liquor from the mother. In adults the usually accepted

theory is that urobilinogen is formed from bilirubin by the action of the intestinal flora (Watson, 1951) but as the foetal gut is sterile it is necessary to postulate an alternative site of formation. With (1951) states that urobilin IXa (mesobilene-b), a substance easily confused with urobilinogen, may be produced extra-enterally, but only traces of this substance are found in the liquor, and further work is required to determine the site of formation of the urobilinogen.

The concentrations of bilirubin and biliverdin are of no value in assessing the prognosis for the foetus but the icteric index has given a sure guide to the development of kernicterus if the reading is corrected for the amount of bilirubin and biliverdin present (Fig. 2). Above a critical level kernicterus has always occurred. Isolation of the pigment responsible for the additional colour has been difficult but its extraction and its properties agree with the findings of Rimington and Stewart (1932) and it appears to be a dipyrrole pigment, mesobilifuscin. Further consideration of this pigment will be given in a future publication.

The idea that kernicterus is primarily a foetal as opposed to a neonatal disease will not be generally accepted as stillborn hydropic foetuses do not show evidence of kernicterus. This objection is not altogether valid, as the placenta must play a large role in the metabolism of the foetus while the neonate is deprived of its support. In this connexion it must be mentioned that I have found nothing to support the findings of Velez Orozco *et al.* (1950) that the maternal serum bilirubin is raised in haemolytic disease of the newborn. Examination of the brains of 5 cases of kernicterus has shown that there is no bilirubin or biliverdin in the yellow areas, but that there are appreciable amounts of pentdyopent and mesobilifuscin.

It must be stated that the development of kernicterus is unrelated to the degree of anaemia of the infant and quite unrelated to the iron content of the liquor.

The presence of porphyrins in the liquor should throw some light on the mechanism of haemoglobin breakdown, although it is unlikely that they produce symptoms, as their concentration is so small. If the disease were one purely of haemoglobin breakdown, coproporphyrin III would be found in excess (Lemberg and Legge, 1949), but the substance present in greatest amount is the I isomer, indicating that there is some interference with haemoglobin synthesis. As yet no explanation can be given of this finding.

The theoretical implications of the investigation are interesting enough, but their practical application will be of use in the individual case of Rhesus sensitization. It is suggested that all cases where Rhesus antibodies are found in the blood should have specimens of liquor withdrawn during the last trimester of pregnancy and, from the concentration of iron and a consideration of either the urobilinogen concentration or of the icteric index and bilirubin concentration, a sure idea of the prognosis for the foetus can be obtained. All these tests are within the capabilities of a small laboratory and there can be no real excuse for not doing them.

Summary

The results of the analysis of 205 specimens of liquor amnii taken from 98 patients in the antenatal period are presented. These results show that the composition of liquor is variable but that help is obtained in the prognosis of haemolytic anaemia of the newborn from consideration of the concentration of the non-haematin iron, disease of the foetus producing an increase in the concentration.

A fall in the concentration of urobilinogen is connected with an increase in the icteric index of the liquor not due to bilirubin, and is followed by the development of kernicterus in the foetus. It is suggested that this onset of kernicterus is due in some way to the presence of mesobilifuscin.

These findings taken together offer considerable help in the assessment of the individual case of Rhesus sensitization.

Thanks are due to the trustees of the Leverhulme Research Fund and the Royal College of Obstetricians and Gynaecologists for a grant to pursue this investigation; to the Consultant Medical Staff at St. Mary's Hospitals, Manchester, for referring cases for study; to Professor W. F. Gaisford for access to the babies and for much help; to Dr. J. E. Kench for sup-

plies of coproporphyrin and for information about haemoglobin and the bile pigments; above all to the resident medical and nursing staff and to the patients for their forbearance with my demands.

Appendix

Technique. Details of the technique for abdominal paracentesis and for the preparation of glassware and reagents have been given by Bevis (1952).

Bilirubin. The majority of the estimations have been by the diazo method described by King (1951). Parallel estimations by the methods of Malloy and Evelyn (1937) and Peterman and Cooley (1933) show slight differences due to the presence of biliverdin.

Biliverdin. As there is no direct method for measuring the amount of biliverdin in a mixture with bilirubin, an attempt has been made to estimate the concentration from the difference between the diazo and oxidation estimations of bilirubin. This is open to criticism and in very doubtful cases the total pigments have been estimated by the method of Gardikas, Kench and Wilkinson (1950).

Chlorides. The method of King (1951) as described for cerebrospinal fluid.

Cholesterol. The colorimetric method of Lieberman and Burchard as described by King (1951).

Coproporphyrin. The total concentration has been estimated by the method of Schwartz, Zieve and Watson (1951), using a photo-electric fluorimeter modified from Rimington (1943). A pure coproporphyrin standard was kindly supplied by Dr. J. E. Kench of Manchester Royal Infirmary.

Isomer analysis has been performed by the method of Schwartz *et al.* (1947), using their original procedure.

Haemoglobin. The values for cord haemoglobin have been obtained by the resident paediatric staff, using an M.R.C. neutral wedge photometer. All values are on the Haldane scale (100 per cent = 14.8 g. per 100 ml.).

Icteric index. A photo-electric method has been devised, using the difference between the extinctions of centrifuged liquor, using Ilford filters Nos. 622 and 626. This method appears accurate enough for clinical use.

Iron. The method has been described in a previous publication (Bevis, 1952). The standard used contains 100 μg. iron per 100 ml. The saturation limit was measured by procedure B of Laurell (1947) using the thiocyanate method for the final estimation.

Copper. A minor modification using smaller quantities of liquor and reagents has been evolved from the method of Cartwright, Jones and Wintrobe (1945).

Protein. The total concentration has been estimated by the colorimetric method described by King (1951).

Sugars. Glucose has been measured by the colorimetric method of King (1951), fructose by the method of Bacon and Bell (1948), pentose by the method of Green, Hopewell and Threlfall (1951).

Urea. The colorimetric method of King (1951) for blood has been used.

Urobilinogen. The method of Watson (King, 1951) has been used; 0.5 ml. of liquor are used and the volume of other reagents reduced proportionately. The standard used is Terwen's. Urobilinogen IXa has been estimated by the method of Lemberg, Lockwood and Wyndham (1938).

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MASCULINIZATION OF OVARIAN ORIGIN

Report of a case with virilization developing during pregnancy

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MASCULINIZATION of the adult human female may result from the presence of a biologically active ovarian tumour. The distinction between the so-called adrenogenital syndrome, benign hirsutism and true defeminization with virilization may be difficult clinically. Biological and chemical assay methods for the various hormones are likely to be the most useful adjuncts to clinical diagnosis. The interpretation of the morbid anatomical changes producing virilization has progressed recently. Of the ovarian tumours responsible, the general group described by Robert Meyer (1931) as arrhenoblastoma is the commonest. A second group referred to by Barzilai (1943) as "virilizing lipoid-cell tumours" includes the neoplasms described by other authors as hypernephroid or adrenal-rest tumours of the ovary. Iverson (1947) has reviewed these tumours at length. A third very rare group of tumours, originally described by Berger (1942) and recently reviewed by Sternberg (1949), is that arising from ovarian hilus cells.

Fraenkel (1943) described virilization produced by a diffuse hyperplasia of theca cells and referred to it as thecomatosis. Selye (1945) referred to this condition as "testoid hyperthecosis" to distinguish it from a similar process producing feminizing signs which he called "folliculoid hyperthecosis."

The case reported here is considered significant in that masculinization developed during an otherwise normal pregnancy. This is extremely rare whatever the pathological basis for the masculinizing effect, which in this case is considered to result from an abnormal development of the theca luteal cells with the formation of giant bilateral ovarian cysts. Surgical removal of these ovarian cysts resulted in a dramatic return of normal female sex characteristics.

CASE REPORT

A married white female, aged 24 years, was first seen on 1st May, 1951. She gave a history of having first become pregnant in July, 1950. All was apparently normal until 15 weeks, when, following a cold, her voice became gruff and remained so. In January 1951 she noticed the hair on her face was becoming profuse. This new growth of hair was mainly on the side of her face and little grew on the chin and upper lip. It was necessary to shave every 3–4 days. For several months she had been troubled with acne of the face and forehead.

On 6th April, 1951, following a normal labour, she gave birth to a healthy female child weighing 5 pounds 8 ounces. Following delivery there was very little decrease in the size of her abdomen. The baby was not breast fed only because not enough milk was produced. Nine days postpartum she had an attack of lower abdominal pain which recurred on several occasions later.

There had been no previous illnesses of note. Menarche had occurred at 16 years of age and menstruation had always been irregular, the periods lasting 5–6 days and occurring every 28–56 days. She had no attraction for her own sex although there had been an absence of libido for several months.

Physical examination revealed a small female 4ft. 10ins. in height, 8 stone 12 pounds in weight. The hair on the side of her face was profuse although it had recently been shaved. There was well-marked acne of the face and forehead (Fig. 1). The hair of the rest of her body was excessive and had a male distribution. Her voice was deep and gruff, more so than the average male voice.

Her abdomen was grossly distended (Fig. 2) and striae were visible on the anterior abdominal wall, but they were not pigmented and had no features distinguishing them from the striae gravidarum. The

FIG. 1

Close-up view of face showing growth of hair, especially near angle of jaw, and acne. (Sask. Vis. Ed. Photo.)

FIG. 2
Showing abdominal mass 3 weeks postpartum.
(Sask. Vis. Ed. Photo.)

FIG. 3
Enlarged clitoris 3.5 cm. length × 1 cm. diameter.
(Sask. Vis. Ed. Photo.)

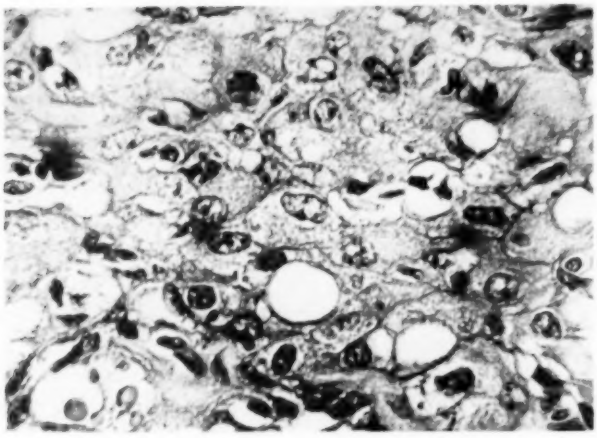

FIG. 4

Granulosa luteal cells of corpus luteum of pregnancy.
H.E. × 510

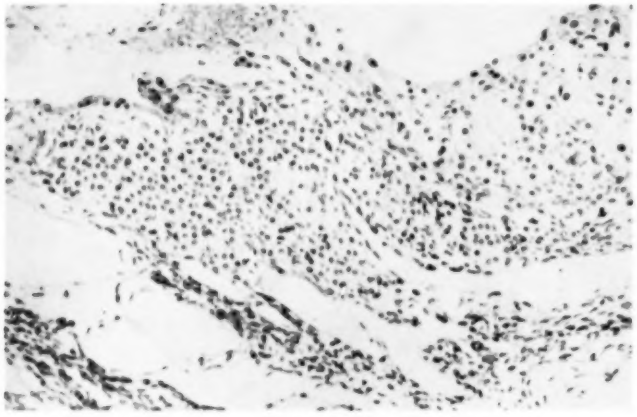

FIG. 5

Wall of cyst showing broad zone of granulosa luteal cells to right of photograph shading into a single layer of columnar epithelium at the left-hand edge. There is a prominent theca luteal zone. H.E. × 148

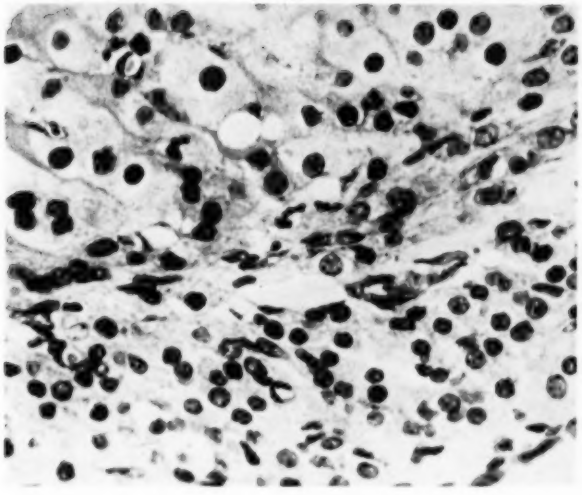

FIG. 6
High-power view of Fig. 5, showing junctional zone between granulosa luteal cells (above) and theca luteal cells (below). H.E. × 510

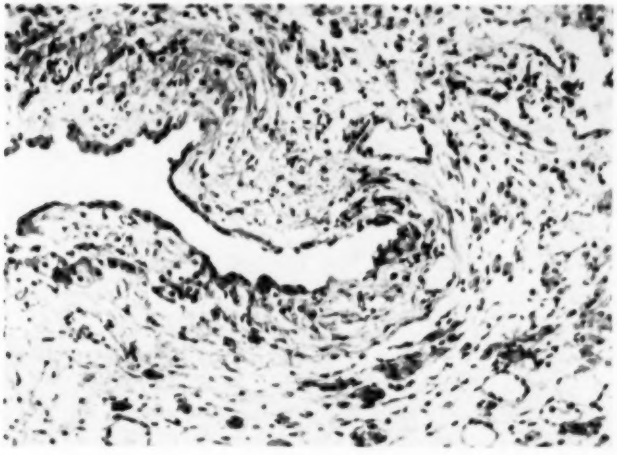

FIG. 7
Wall of cyst showing "epithelial" lining, a zone of connective tissue and isolated theca luteal cells in the surrounding loose tissue. H.E. × 148

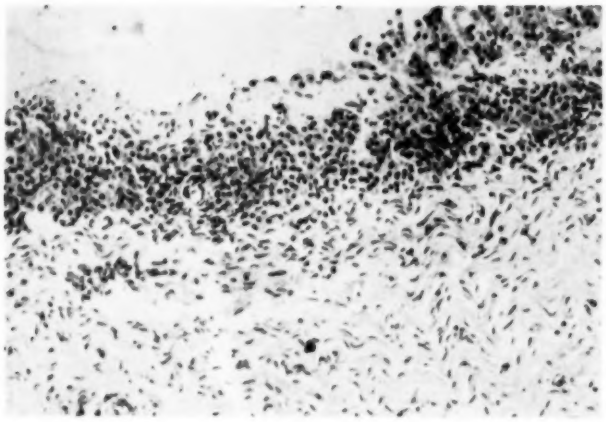

FIG. 8

Showing layer of granulosa luteal cells at right-hand edge shading into a single layer of cubical lining cells. There is a well-marked zone of hyaline connective tissue and a broad theca luteal layer. H.E. ×148

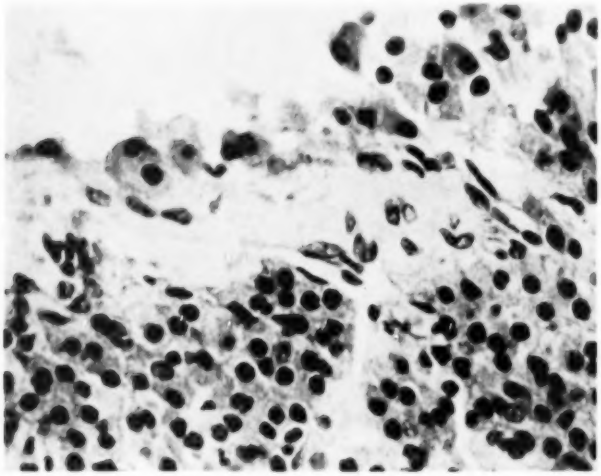

FIG. 9

High-power view of Fig. 8, showing granulosa luteal cells (above) and theca cells (below). H.E. ×510

FIG. 10
Wall of cyst showing well-defined hyaline connective tissue zone. H.E. ×148

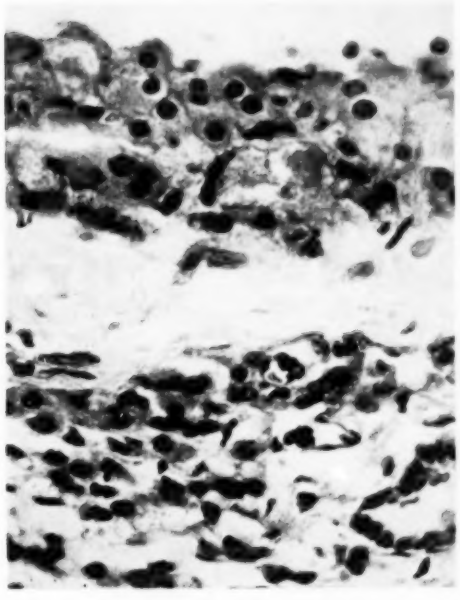

FIG. 11
High-power view of Fig. 10. H.E. ×510

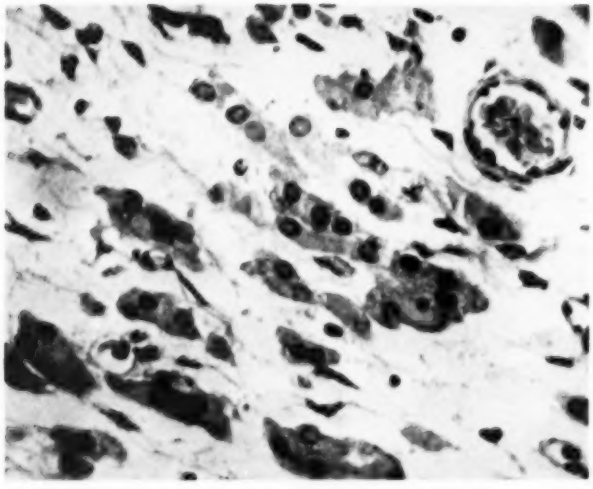

FIG. 12

Scattered theca luteal cells in a loose fibrous stroma; high-power view of Fig. 7. H.E. ×510

abdominal distension appeared to be due to a cystic tumour arising out of the pelvis and filling practically the whole abdomen.

The breasts appeared well developed. The blood pressure was 130/90. Pelvic examination showed a lacerated cervix but the other organs could not be identified because of the mass. The clitoris was enlarged and congested and measured 3.5 cm. in length and 1.2 cm. across (Fig. 3).

Chest X-ray and intravenous pyelogram were normal. Skull X-rays suggested some slight enlargement of the pituitary fossa. The film measurements were: depth 1.1 cm. (maximum normal about 1.1 cm.), A.P. 0.9 cm. (maximum normal about 1.3 cm.).

The 17-ketosteroid excretion on 3rd May (27 days after delivery) was 100 mg. in 24 hours. A repeat estimation 3 days later showed 104 mg. in 24 hours.

A glucose tolerance test showed a rather flat type of curve. Fasting, 74 mg. per cent; 15 mins., 110 mg. per cent; 45 mins, 85 mg. per cent; 75 mins., 88 mg. per cent; 105 mins., 80 mg. per cent; 135 mins., 99mg. per cent.

The blood chlorides were 520 mg. per cent, and the 24-hour urinary chlorides 9.5 g. The blood creatinine was 1.9 mg. per cent.

Serum sodium on 3rd May was 173 mEq/litre (402.5 mg./100 ml.); on 9th May it was 150 mEq/litre (350.0 mg./100 ml.).

Serum potassium on 3rd May was 4.4 mEq/litre (17.0 mg./100 ml.); on 9th May it was 4.5 mEq/litre (17.3 mg./100 ml.).

Blood chloride on 3rd May was 88 mEq/litre (520 mg./100 ml.).

A blood count showed Hb. 14.3 g., R.B.C. 4.18 mil., hematocrit 40 per cent. A white-cell count was 7,700 with a normal differential. The sedimentation rate was 15 mm. in 45 mins. (Westergren). The presumptive Kahn was negative and urinalysis showed a trace of albumen.

On 10th May, 1951, a laparotomy was performed and 2 very large ovarian cysts were found. The right ovary and cyst were removed completely. The left ovary was dissected free from the left ovarian cyst and this remnant of ovary was preserved. Both suprarenals were palpated and appeared to be normal.

The patient's post-operative course was uneventful. Estimation of the 17-ketosteroid excretion 2 weeks after operation showed 3 mg. in 24 hours.

The patient was seen again on 25th July, 1951, 10 weeks post-operative. She had no complaints. The hair on her face had stopped growing and she had shaved only once since the operation. Her weight was still 10 pounds above normal.

On examination the hirsuties had almost disappeared and the acne was much improved. The voice was unchanged. No abnormal physical signs could be found. The measurements of the clitoris were the same but it was no longer congested.

The excretion of 17 ketosteroids on this occasion was 7.6 mg. in 24 hours.

When seen on 6th December, 1951, 7 months after operation, she had no complaints. Two normal menstrual periods had occurred, one during October which lasted 5 days and one just completed which lasted 5 days. There was no excess hair on the face and the patient had not shaved. The body hair was of a female distribution. The acne had disappeared. The voice appeared to be of slightly higher pitch. Pelvic examination was normal and the clitoris measured 2.5 × 1 cm.

On 19th June, 1952, 13 months after operation she was found to have gained 10 pounds in the previous 6 months. She felt well and strong. Her periods had continued to be regular with a moderate flow lasting 4 or 5 days every 30 days. Her voice had not changed but the facial hirsuties had disappeared. She had not shaved since the operation. She still complained of a persistent discharge of milky fluid from both nipples. Milk could be expressed from both breasts on pressure. The clitoris measured 2.5 cm. in its greatest length, but was not congested. X-ray of the pituitary fossa showed the measurements to be unchanged. The 17-ketosteroid excretion was 1.8 mg. in 24 hours.

The baby, now 14 months old, was not seen but was described as well-developed, healthy, and walking.

Pathological Examination

The specimen consisted of 2 very large cystic ovarian tumours. The right ovarian mass weighed 8 pounds 3 ounces (3,724 g.) and measured 14½ inches (37 cm.) in diameter. The left ovarian tumour weighed 3 pounds 7 ounces (1,576 g.) and measured 6 inches (15 cm.) in diameter.

Both masses consisted of large smooth-walled multiloculated cysts filled with slightly turbid yellowish fluid. The walls of the cysts consisted of thin fibrous tissue. At one pole of the right ovarian tumour a compressed and flattened remnant of the right ovary could be identified. This measured 2.5 cm. in diameter and 1 cm. in maximum thickness. Approximately 5 litres of fluid was present in both cysts. This fluid contained 0.1 mg. of 17-ketosteroids in 100 ml.

Microscopic Examination

The corpus luteum of pregnancy could be identified in the right ovary. It showed no histological evidence of regression. The cells were large and polyhedral with eosinophilic, faintly granular cytoplasm (Fig. 4). The cells had either central or peripherally placed large, oval nuclei. A number of very thin-walled blood vessels ran from the central hilar region of the corpus luteum into its peripheral cellular area. The corpus luteum was demarcated by a slight

fibrous condensation of the ovarian stroma around it.

In both ovaries a number of small and large cysts were found. These cysts were lined by a zone of cells which varied in appearance from a multilayered characteristic granulosa cell layer (Figs. 5, 6) to a single layer of cubical or columnar epithelium (Fig. 7). In many instances a transition could be identified in the wall of a single cyst (Figs. 8, 9, 10). In some of the larger cysts the lining epithelium had disappeared entirely. This layer of granulosa cells was only partially luteinized, at least some of the cells had abundant eosinophilic cytoplasm and contained some lipoid (Figs. 8, 11).

Outside this lining zone of cells there was a narrow band of hyaline connective tissue (Figs. 8, 10). In some areas this was no more than a lining membrane between the inner granulosa layer and the theca interna layer (Fig. 6). Elsewhere the hyaline layer was wider especially in the segments where the lining layer was a single layer of cells (Figs. 9, 10).

Outside the hyaline layer was a variable zone of luteinized theca interna cells (Figs. 9, 11). In some segments these cells were arranged as a broad band several cells in thickness (Figs. 5, 6, 8), while elsewhere the cells were more diffusely distributed in a loose layer of connective tissue (Figs. 7, 12). In some of the sections this loose layer of connective tissue containing isolated theca interna cells had extended beyond the immediate environs of a cyst and filled the interval between adjacent cysts or between a cyst wall and the zone of remaining ovarian tissue (Figs. 11, 12).

The identification of these isolated cells as theca interna cells offered some difficulty. They were at first regarded as hilus cells but failure to identify crystalloids in the cytoplasm caused this view to be discarded. Careful study revealed their identity with the theca interna cells lining the cystic spaces.

Discussion

The production of masculinizing signs in a previously normal female may result from the presence of a hormonally active ovarian tumour. Some such tumours have been regarded as arising from cells which are not normal constituents of the ovarian stroma but are aberrant adrenal islands. These tumours have been called "hypernephroid" or "lipoid cell" tumours. Another group of tumours arises from the hilus cells which were described by Berger (1922). They form a group of cells usually closely related to nerves and blood vessels in the hilum of the ovary. Berger subsequently described adenomas arising from these cells which had produced masculinizing signs.

Sternberg (1949) in a complete review of these cells and their androgenic properties, described 2 cases of tumours with masculinization as well as 2 instances of hilus cell hyperplasia also associated with masculinization. In a footnote this author referred to 1 additional example of tumour and 2 of hyperplasia seen since submission of his paper.

Sachs and Spiro (1951) describe a case of hilus cell tumour of the ovary with masculinizing symptoms. This case died of carcinoma of the lung, and the case report includes the autopsy findings, apparently the first of the cases hitherto described to have a postmortem examination. Earlier cases described in the literature include one reported by Dreyfuss and Barrozo do Amaral (cited by Berger, 1942), where the pathological picture was obscured by the presence of an adrenal tumour. Cosasesco *et al.* (1931) and Giordano and Haymond (1944) have reported cases which are referred to by Sachs and Spiro as having been placed in this group by Berger. Waugh, Venning and McEachern (1949) have also described 1 case where Berger agreed with the diagnosis.

Thus 9 cases of tumour and 4 instances of hyperplasia of these cells are found in the literature.

The recognition of hilus cells has usually depended on their appearance in stained sections and especially upon the indentification of the crystalloids of Reinke in their cytoplasm. The characteristic appearance is that of a large polyhedral cell with eosinophilic granular cytoplasm, frequently described as appearing like an interstitial cell of the testis or like a liver cell. The cells are arranged in small groups closely investing a capillary vessel and there are usually nerve twigs present. The characteristic tumour arising from these cells is a small yellow or brown nodule seldom more than 2 cm. in diameter, well encapsulated with some areas of haemorrhage.

The confusion in the recognition of these cells, however, is well illustrated in our case where several authorities consulted at first regarded the unusual cells as hilus cells but subsequently agreed with their identification as theca interna cells. This confusion has also been noted in connection with the interpretation of cells which have been found in the stroma of other tumours. Brentnall (1945) referred to the tumour in his case as an arrhenoblastoma and the microscopic report specifically identifies epithelial cells which " resemble the interstitial (Leydig) cells of the testicle ". Bell (1915) reported a case of masculinization due to an ovarian tumour and described Leydig cells in a mass which he regarded as an ovotestis. Kanter and Klawans (1924) described a tumour which they called a teratomatous arrhenoblastoma in which Leydig cells were recognized.

Kanter and Klawans continued in their discussion to state: " The Leydig cells are capable of producing large amounts of sex hormone, so that relatively few of them in a tumour can obtain mastery over the ovarian function. The amount of defeminization and masculinization in any given case depends directly on the activity of the existing Leydig cells. Because of this, no matter how highly specialized the tumour may be microscopically, the clinical symptoms produced are directly proportional to the number and activity of the male-hormone-producing cells ".

Hartz (1945) described cells resembling liver cells containing pigment granules which he referred to as interstitial cells.

The importance of the case described here is that the cells responsible for the clinical changes are of ovarian stromal origin. The " interstitial cells " described by other authors could theoretically be derived from the ovarian hilus cells, from theca interna cells which are of stromal origin, or from hypothetical testicular equivalents of teratomatous origin. The concept of origin from the ovarian stroma itself under the stimulus of the presence of a tumour or under some abnormal hormonal stimulus, possibly from the anterior pituitary or from the adrenal cortex, renders it unnecessary to postulate an origin from adrenal rests or from any other unusual group of cells which are difficult if not impossible to find in the normal ovary.

Glynn (1921) reviewed the subject of " ovarian hypernephroma " and " suprarenal virilism " resulting therefrom and concluded that these tumours are of luteal origin rather than from suprarenal rests. This author referred to the association of typical suprarenal virilism with ovarian tumours as described by Apert and Pozzi. In Apert's group of 5 cases masculinization was associated with ovarian cystic tumours but the protocol is incomplete in that no reference was made to recovery after operation and the suprarenals were not examined.

Selye (1945) considers that the lipoid cell tumours should be regarded as a single entity until proven otherwise and further considers that most of them arise from adrenal rests although an origin from the corpus luteum cannot be denied.

The case of Hobbs (1949) is of interest in that the tumour was partly arrhenoblastoma with Leydig cells and partly diffuse granulosal or thecomatous tumour. This patient showed slight virilization and also some features of feminizing influences. The author believes the 2 tumours developed simultaneously in the same ovary and each exerted some hormonal effects. Hobbs called his tumour gynandroblastoma. Hobbs's case is similar in its essential features to the case described by Mechler and Black (1943). These authors review the subject of gynandroblastoma at some length. They summarize 21 cases of this tumour collected from the literature. In some of these the presence of " interstitial cells " is specifically mentioned. One case which they quote and which was originally described by Felicissimo Paula Xavier and de Abreu Junqueira illustrated androgenic effects during pregnancy. Removal of the ovarian tumour in this case, however, was followed by accentuation of the masculine changes.

Mechler and Black (1943) quote Bergstrand who rejected all earlier theories which ascribed hirsutism to the internal secretion of tumours arising in an hypothetical testicular component of the embryonic ovary. He found no indication from his studies whether the hormone is produced by the granulosa or the lutein cells of the tumours but subscribed to the theory of Steinach and Kun that the hormone comes from the lutein cells.

The condition described by Fraenkel (1943) is closely related to the situation found in the case reported here. Selye and Collip (1933) produced theca luteinization experimentally by the administration of anterior pituitary gonadotrophin and found that this was accompanied by virilization in the animals. Selye further commented upon the relationship between these luteinized cells and the hilus cells and stated " the relationship is rather problematic in spite of superficial morphologic similarity ".

Geist and Gaines (1942) report 2 cases of masculinization accompanied by bilateral ovarian enlargement due to excessive perifollicular proliferation and luteinization of the theca cells, and diffusely scattered luteinized cells within the ovarian parenchyma. These authors consider the ovarian effects were suggestive of increased gonadotrophic stimulation and are probably secondary. These cases are apparently similar to the case described here.

Turner (1943) describes a case of masculinization in which both ovaries were enlarged with widely scattered follicular cysts containing clear mucinous fluid. Most of the follicular walls contained a well-defined narrow granulosal layer with a much wider well-developed theca interna showing distinct luteinizing characteristics. The stroma was dense and contained clusters of lutein-like cells at some distance from the follicles. Wedge resection of the ovaries produced much benefit. No hormone studies were carried out.

Traut and Marchetti (1940) analyzed 61 granulosa and theca-cell tumours. Only 2 of these cases showed masculinization with hirsuties, male voice, hypertrophy of the clitoris, atrophy of the breasts and amenorrhoea. One of these cases had a tumour of the folliculoid type, with a structure simulating the structure of a Graafian follicle, and was regarded as an undoubted granulosa cell tumour and this patient recovered after removal. The other case was of cylindroid structure with groups of large cells in islands. These cells were of granulosa type with luteinization common in some degree. These authors continue that " it is safe to say that no one today believes that the Graafian follicle tumours originate from the differentiated follicle, the corpus luteum or even the atretic follicle ". Whether such a denial applies to the hyperthecosis of Fraenkel is not clear.

King (1931) described luteal cysts of follicular origin as being of two principal varieties. One type shows well developed theca interna and an extremely poorly marked stratum granulosum layer. In the second type, representatives of both layers are well marked. King states that large cysts may develop from atretic follicles.

Multiple luteal cysts are commonly associated with hydatidiform mole and it is generally considered that a hormone from the pituitary gland plays a part in the causation of these multiple cysts.

A number of cases have been reported in which massive ovarian cysts have been associated with masculinization. The case of Kanter and Klawans (1940) presented as a giant cystic mass filling the abdomen. Hartz (1945) reported a giant cystic arrhenoblastoma containing entodermal epithelium and a carcinoid removed from a woman with typical hirsutism and clitoral hypertrophy. The author describes cells resembling liver cells containing pigment granules, which he refers to as interstitial cells.

Bilateral polycystic ovaries were found in a series of cases reported by Stein and Leventhal (1935). The subjects showed some features of defeminization, viz., amenorrhoea and sterility, and a few showed masculinization changes. These cases were relieved by wedge resection of the ovaries. The cysts, of follicular origin, were considered to arise from some anterior pituitary dysfunction, and no evidence of significant cellular changes was seen in the ovarian tissue. Baldwin and Gafford (1936) reported a case of masculinization due to a large multiloculated cystic poorly differentiated arrhenoblastoma, but no mention is made of hilus cells.

The development of masculinization in the course of pregnancy is extremely rare. In most instances amenorrhoea and sterility are early features, but there is no reason why the virilization should not begin during or following pregnancy as a coincidence (Brentnall, 1945).

Baird and Astwood (1946) recorded the dramatic onset of masculinization in a woman of 24 years during the 4th month of her first pregnancy. These features persisted through 3 additional pregnancies. No specific diagnosis was established in this case.

Culiner and Shippell (1949) refer to a case where virilization occurred during the later months of pregnancy. Both ovaries were found enlarged at Caesarean section, but regressed spontaneously after delivery and 8 months postpartum were of normal size.

Searle, Haines and Baker (1948) describe a case of virilization developing at 24 weeks of a first pregnancy. This was considered to be due to an adrenal-like tumour of the ovary.

In Brentnall's case the foetus was considered to be a female pseudohermaphrodite, though conclusive proof of this was lacking. As far as can be determined from the literature, the other cases have produced normal children of both sexes.

The effect on lactation is apparently variable. In the case of Searle *et al.* lactation was never established. In our case lactation was apparently never adequate for breast-feeding, but some secretion occurred from both breasts and persisted for several months.

A number of authors have studied the hormone excretion in their cases. In our case an initial 17-ketosteroid level of 100 mg. in 24 hours fell within 10 days of operation to 3 mg. and remained within a low normal range. In the case of Searle *et al.*, the 17-ketosteroid excretion prior to delivery was greatly elevated to 158 mg. per day. Three weeks after delivery the daily excretion had fallen to 23 mg., and 8 days after removal of the ovarian cyst it decreased still further to 12.8 mg. Sachs and Spiro's case showed no increase in 17-ketosteroid excretion, the chorionic gonadotrophin was "not greatly increased" and the urinary follicle-stimulating-hormone excretion was also low. No increase in 17-ketosteroid excretion was noted in the cases by Culiner and Shippell, Hobbs, Sternberg, and in the syndrome described by Stein and Leventhal. Waugh *et al.* give a daily excretion in their case of 22.8 mg. of ketosteroids, falling after operation to 10.6 mg.

It is clear, therefore, that the excretion of ketosteroid does not provide a clear distinction between the various causes of virilization. In so-called idiopathic or simple hirsutism, Venning and Browne (1947) report values ranging from 23.1 mg. to 37 mg. in 4 cases. They found the glycogenic corticoid values normal or only slightly raised. Koets (1949) measured the excretion in 9 cases of idiopathic hirsutism at weekly intervals during complete menstrual cycles. A cyclic variation was demonstrated, with a maximum excretion at the approximate time of ovulation in contrast to the relative constancy of excretion in normal women.

In the cases thus far reported the results of hormone assays have been variable. It is clear that further study is necessary, and any further cases should be studied exhaustively in the preoperative period.

The clinical examination of a case of masculinizing ovarian tumour does not appear to be able to indicate the nature of the tumour with any certainty. On clinical grounds the distinction between adrenal and ovarian virilism may not be possible. In cases such as ours with a high preoperative 17-ketosteroid excretion, the adrenal cortex appears the organ most likely to be responsible. In our case, however, the very prompt fall after ovarian cystectomy is regarded as adequate proof of a primary ovarian disorder.

There is adequate experimental and clinical evidence to indicate that only a minor difference in activity of ovarian endocrine secretion can result in masculinizing influences as well as defeminization. The cases described by Geist and Gaines, the tumours referred to by Traut and Marchetti and the case reported here all emphasize that abnormal luteal activity may be the cause of a masculinizing syndrome accompanied by a considerable increase in 17-ketosteroid excretion.

Careful examination of all cases of masculinizing ovarian tumours is indicated to determine the precise nature and origin of the cells variously described as "interstitial cells" or "Leydig equivalents". It is suggested that many of these cells may be of ovarian stromal origin or may be derived from the theca interna. The demonstration of crystalloids of Reinke would identify the cells as hilus cells. It is probably wrong to endeavour to identify these cells on the basis of superficial morphologic similarity, as of adrenal origin.

The association between pregnancy and masculinization of ovarian origin is of some significance. Multiple luteal cysts are known to follow hydatidiform mole but in this case the pregnancy reached full term and no suggestion

of hydatid degeneration was seen in the placenta at the time of delivery.

In the present state of our knowledge, however, we must assume that the clinical features in this case resulted from a strong androgen stimulus arising in the theca luteal cells. This was probably initiated and maintained by the anterior lobe of pituitary gland whose normal hormonal activity may have been upset by the pregnancy.

Summary

(1) A case of theca-luteal tumours of the ovaries associated with masculinization is reported. The tumours were bilateral and appeared as large polycystic masses filling the abdomen.

(2) The case reported is unusual in that the signs of masculinization developed at about the 4th month of pregnancy. This appears to be the fifth case on record where virilization due to an ovarian tumour has coincided with pregnancy.

(3) The literature concerning masculinization of ovarian origin has been reviewed.

(4) It is suggested that the theca interna cells may be more frequently responsible for masculinization either alone or in association with other tumours than has been recognized in the past. The recognition of this possibility renders it unnecessary to invoke cell nests of adrenal or other origin in the interpretation of ovarian tumours.

We wish to thank Dr. J. B. Ritchie, for referring this interesting case; also Mr. H. E. Robertson, director of Saskatchewan Provincial Laboratory, for the 17-ketosteroid estimations.

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CRUSH FRACTURE OF THE DORSAL SPINE IN ECLAMPSIA*

BY

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CASES of fracture of the dorsal spine occurring during artificially induced convulsions have been described for many years. In this paper it is intended to deal with the literature on this subject and to record and discuss a case of crush fracture of the dorsal spine complicating eclampsia.

In 1907 Lehndorff first described the bony injury to the dorsal spine following convulsive seizures of tetanus, but it was not until 1938 that this subject became of real importance when Stalker recorded in the *Lancet* a single case of vertebral fracture in convulsion therapy. This coincided with Wespi's (1938) account in Germany and since then a large number of articles have appeared describing this condition.

Polatin, Friedman, Harris and Horwitz (1939) concluded that 43.1 per cent of all cases treated by convulsions induced by metrazol sustained spinal damage, while Worthing and Kalinowsky (1942) and Meschan, Scruggs and Calhound (1950) estimated that 35.4 per cent of convulsion therapy cases sustained vertebral body injury and that two-thirds of these occurred during the first three treatments. Easton and Sommers (1944), in a review of 800 cases of metrazol convulsions, found an incidence of 26.1 per cent, whilst Horwitz (1944) aggregated an incidence of 20 per cent.

Though there appears to be some variation in the incidence recorded, all workers, however, agree with Worthing and Kalinowsky (1942) " that fractures in electric shock therapy were a quarter as frequent as fractures in convulsions induced with metrazol ".

Compression fractures of the dorsal vertebrae in tetanus and in convulsion therapy have, therefore, been recognized for a long time and, since Pearson and Ostrum (1940) demonstrated a similar fracture with insulin coma treatment, it is reasonable to expect identical changes in epilepsy. The literature, however, is confused on this point but the consensus of opinion now is that about 33 per cent of epileptic patients sustain dorsal vertebral fractures. This is found to be in line with the findings of Reed and Dancey (1940), Cook and Sands (1941), Moore, Winkelman and Solis-Cohen (1941), Barrett, Funkhouser and Barker (1942), and Caplan (1946). The last worker, after a careful study, concluded " that the fractures in epilepsy are, *mutatis mutandis*, of the same type and distribution as those resulting from convulsion therapy, and that their incidence is comparable to that resulting from metrazol therapy ". It is probable that what difference there is, is due to the fact that the lesions in epileptics are much older and have undergone secondary changes.

All workers are agreed that the location of the fractures is in the region of the 4th to the 8th dorsal vertebrae, the commonest of these, according to Easton and Sommers (1942), being the 4th, 5th and 6th, the most frequently affected being the 5th. This type of fracture involves the body of the vertebra only and varies from a mild depression of the superior plate to a considerable compression and crushing of the vertebral body anteriorly, resulting in a wedge-shaped deformity.

It is, therefore, established that tetanus, convulsion therapy and epilepsy can give rise to crush fracture of the dorsal spine, so it might be expected that a similar injury would complicate eclamptic convulsions. The eclamptic convulsion has been described by Macintosh (1952) as " not differing from those of so-called

* Read at a Meeting of the North of England Obstetrical and Gynaecological Society, held in Manchester on Friday, 24th October, 1952 (see p. 268).

ether convulsions, seizures of certain children suffering from tapeworm or pyrexia, attacks of idiopathic epilepsy, nor from the violent muscular response to therapeutic electric shock," so it is a legitimate assumption that a comparable incidence of spinal fractures would be sustained with eclamptic attacks. However, a review of the literature reveals only one such recorded case. This was described from the Radiological Department of the Drammen Hospital, Norway, by P. M. Kielland in 1947. He records a case of a primipara, aged 28, who had 2 postpartum eclamptic fits with loss of consciousness, one of which occurred after admission into hospital. She subsequently complained of pain between the scapulae and was X-rayed. This showed that the 6th dorsal vertebra was wedge-formed and subsequent examination revealed a tenderness over the spinal processes of the 5th and 6th dorsal vertebrae. He rightly concludes " this fracture is similar to the fractures observed after shock therapy and tetanus ".

The following case also illustrates that compression fracture of the spine can result from an eclamptic attack.

A primigravida (Record No. 13962), aged 24, with no previous history of illness or injury, was admitted in labour to a small general practitioner maternity home at 10 p.m. on 16th May, 1952. At 11 a.m. the following day she had an eclamptic fit and was delivered with forceps at 1 p.m. by the general practitioner. One hour later she had a second convulsion and was transferred by ambulance to our maternity hospital, a distance of 30 miles. During transit, and when 4 miles from the hospital, she had a third fit and was comatosed on admission.

When examined she was found to have a raised blood-pressure, marked oedema and considerable albuminuria, but she rapidly recovered from this immediate emergency, with the minimum of treatment and without having any further fits. The day after delivery she complained of pain in the back, at the level of the scapulae; this was not severe and caused no distress. As the pain persisted on the 4th day of the puerperium and as the clinical findings were negative an X-ray examination of the chest and spine was made.

The X-ray revealed fractures of the 4th, 5th, 7th and 8th dorsal vertebrae, which resulted in partial wedging of these bodies, with an increasing kyphosis. These were of recent and of traumatic origin (Figs. 1 and 2).

We were advised that no treatment was necessary and she was discharged from hospital 3 weeks after her confinement.

The patient was again seen 3 months later and she now complained of only occasional backache over the mid-dorsal spine, but her spinal movements were normal and painless.

Discussion

The theories propounded by Lehndorff (1907), Erlacher (1920), and Roberg (1937), that muscle force caused the vertebral compression in tetanic convulsions are accepted as applying also to other convulsive fractures.

The opinion of Worthing and Kalinowsky (1942) is that the mid-dorsal curvature becomes subjected to strong converging muscular forces, which act above and below the dorsal region.

Easton and Sommers (1942) explain that the spinal extensor muscles are weak over the mid-dorsal area, so that this point offers the least resistance to the converging muscular contractions of the anterior muscles—including the abdominal group—resulting in an anterior bowing action, consequently bending the spine acutely in the mid-dorsal region.

The upper dorsal spine has been described by Pearson and Ostrum (1940) as the least flexible of the vertebral column and Meschan *et al.* (1950) have demonstrated that in this region there is a maximum normal kyphosis. This area, therefore, is at a disadvantage when subjected to any violent muscular contraction that causes excessive flexion of the spine, thus frequently resulting in collapse of the vertebral body. Caplan (1946) states that susceptibility is associated with individual peculiarities of convulsive pattern and that the majority of fractures occur among those patients whose fits usually take place in an attitude of flexion. He concludes " that other things being equal, a patient's liability to fractures depends on his individual convulsive pattern—some have fits in a predominately flexed posture and others have convulsions in extension, while others are intermediate in pattern. Fractures were present in the ' flexion class ' and absent in the ' extensor class ' ".

It is further agreed by Wespi (1938), Friedman, Brett and Vogt (1940), Caplan (1946), and others, that conditions suitable to cause these fractures may occur at any phase of the con-

FIG. 1

Wedging of the 4th, 5th, 7th and 8th dorsal vertebrae.

O.V.J.

FIG. 2

Cone view

vulsion, not only at the acute flexion spasm at the onset of the seizure but also during the tonic and clonic stages of the fit.

The localization of the fractures in this case and Kielland's case, occurring after a convulsive attack, appears to confirm that the fractures were caused by the bowing action of the muscular spasms in an eclamptic fit. Both patients had, at least, one severe convulsion leading to unconsciousness and an additional common factor in these 2 cases is that both had intense fits in the postpartum phase. A full-time uterus can be expected to prevent excessive anterior bowing action of the spine during these spasms; and already, of course, the spine of the expectant mother has a normal tendency to hyperextension. It may, therefore, be concluded that the fractures occurred in this recorded case (as in Kielland's) during the severe postpartum fit and not during the antepartum convulsion.

All workers attempt to minimize the bowing action of the muscular spasms of convulsion therapy. Thus, Cheney, Hamilton and Heaver (1941), Easton and Sommers (1942), and Meschan *et al.* (1950), found that having the patient inclined on the table or bed with the back hyperextended reduces the incidence of the fractures. This position is natural for the expectant mother, so that such precautions should only be emphasized during postpartum eclampsia.

Modification of the muscular spasms in convulsion therapy by administration of curare has been recommended by Easton and Sommers (1944), Cummins (1942), Meschan *et al.* (1950), Schega (1950), and Sonnenshein (1951), and all demonstrated a fall in the incidence of fractures varying from 15 to 20 per cent. They emphasized that curare should not be administered in such a concentration as to paralyze respiration and that it must be given from the start of the convulsion. This latter condition can be fulfilled in convulsion therapy when the fit is induced, but not in eclampsia where the spasms are insidious in onset. In addition curare used in conjunction with the deep sedation associated with the treatment of eclampsia would entail considerable risk.

The case recorded here complained of localized backache over the mid-dorsal area of the spine and this appears to be characteristic of the condition. Caplan (1946) found no record of any serious complication of the fractures and Cook (1944) stated that " they are not followed by serious sequelae and have proved to be far less important than was at first stated ". In fact, the degree of subjective complaint is extremely mild compared with the pathology present. This, of course, is so because the fractures affect the part of the spine which is devoid of anterior-posterior movement, so that changes in the contour of these vertebral bodies are of little significance. They, therefore, rarely need any treatment and, as in this recorded case, the pain soon disappears and the recovery is complete.

Other predisposing factors in the spine were not found by Easton and Sommers (1942) to influence the incidence of fractures and Pearson and Ostrum (1940) are of the opinion that there was no evidence of interference with the phosphorus or calcium metabolism in their cases. It can, therefore, be assumed that pregnancy as such does not predispose to a tendency to fractures, but that, in fact, a convulsion before confinement, with the spine in a state of extension, is less likely to cause a fracture than is a convulsion after delivery.

It was decided to review some patients who had suffered from eclampsia during the last few years. In the time available 30 cases were X-rayed; 20 of these had antepartum eclampsia and 10 were postpartum in type. No case of either group revealed evidence of any degree of wedging of the dorsal vertebrae. The other findings, such as 5 with slight scoliosis of the dorsal spine and 5 with osteoarthritic lipping, cannot be associated with any trauma caused by the convulsive seizures.

Only 5 complained of back pains in the dorsal region and all these showed slight osteoarthritic lipping.

It is also noteworthy that, of the postpartum group, only 2 suffered transient loss of consciousness, otherwise all the attacks were mild. This suggests that the fits were not sufficiently violent to produce excessive anterior bowing of the spine.

The 2 postpartum convulsions in this recorded

case were very intense and there can be no doubt that the compression fracture described is analogous to the fracture demonstrated after convulsion therapy, epilepsy, and tetanus. Both the localization and the wedging of the vertebrae indicate that the mechanism is the same.

It appears reasonable to suggest, in view of these 2 cases of spinal fractures following eclampsia, that X-ray examination of the spine should be performed more frequently after post-partum eclamptic convulsions, when a patient subsequently complains of back pains. These pains should not be accounted for as merely due to muscular strain without ruling out a vertebral injury.

To the orthopaedic surgeon, therefore, eclamptic convulsions join the list of causes of crush fracture of the spine and to the obstetrician this fracture becomes another complication of eclampsia.

SUMMARY

(1) A case of crush fracture of the dorsal spine in eclampsia is recorded and discussed.

(2) The literature concerning crush fracture of the spine in convulsive therapy is reviewed.

My thanks are due to Dr. William Griffith, Dr. P. H. Whitaker, and Mr. G. I. Roberts for their help with this case.

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ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

A MEETING of the Council was held in the College House on Saturday, 31st January, 1953, with the President, Mr. A. A. Gemmell, in the Chair.

The following were awarded Leverhulme Research Scholarships for 1953:

Douglas Charles Aitchison Bevis
Ian Donald
Ian Macdonald

The following were elected to the Membership:

Douglas Macbean Brodie
Patrick Bruce-Lockhart
Donald Stewart Burris
Keith Gordon Cockburn
Sydney Bradfield Cooper
Janette Galloway Cowie
Hendrik Jacobus Greyvenstein de Villiers
Harold Geoffrey Dixon
Margaret Mary Downes
Errol Mendus Edwards
Jack Raymond Elliott
Alan Harvey Foate
Graham Stanley Foster
Alexander Ewing Fyfe
Glyn Haydn Garfield
James Malcolm Gate
Gerald Lynch Gleeson
Louis Goldman
Nigel Gordon Gourlay
Michael Grant
Robert William Grayburn
Joseph Masters Holmes
George Charles Stewart Hunter
Valentine Margaret Husband
Sarah Isaac Jacob
Robert Austin Kenihan
Kamala Khadenga
Hector Howard Kirk
Bernard Vance Kyle
James Comrie McCawley
John Macpherson
James Samuel McVeigh
Jean Murray-Jones
Terence James Murphy Myles
Lloyd Meynell Norburn
Edward Michael O'Dwyer
Selvam Panchalingam
Raymond Marcus McKenzie Pratt
Michael Joseph Maurice Solomons
Wilfred Keith Sutton
Thomas Alexander Thompson
Roger Sinclair Wurm

REPORTS OF SOCIETIES

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

JUNE 1952

A meeting of the North of England Obstetrical and Gynaecological Society was held in Newcastle on Friday, 6th June, 1952. Mr. P. Malpas, the President, was in the chair.

Mr. P. Malpas showed a colour film illustrating

AN INVERSION OF THE UTERUS

The patient, who was 65 years of age, was found to have a complete inversion of the uterus with the vagina showing a considerable degree of ulceration. She had had a vaginal repair operation carried out by the late Professor Leith Murray some 30 years previously and did not know when the present trouble had started. The inversion was treated by vaginal hysterectomy. The mounted specimen was demonstrated.

Discussion

Mr. Eric Stacey considered that this was probably a case of chronic inversion of the uterus, of many years duration, to which the visible prolapse was secondary.

Dr. R. Newton described a case of inversion of the uterus which he had been asked to see by the staff of the Radium Institute where treatment as a case of carcinoma of the cervix had been attempted. The case was described to him as one of pedunculated fibroid but he found the swelling to be an inverted uterus and had performed vaginal hysterectomy.

Dr. W. Calvert stated that he had also attempted to remove a "fibroid polypus" in a similar manner, but when the surface "skin" began to come away he recognized it as an inversion of the uterus. The exposed endometrium appeared normal on macroscopic and microscopic examination.

Mr. B. Williams had seen a patient 70 years of age who had had a previous vaginal repair and presented the appearances of procidentia. This was found, during the course of operation, to be an inverted uterus, and the diagnosis was confirmed by passing a finger into the depression in the uterus through the pouch of Douglas. He also treated his case by hysterectomy.

In reply, Mr. Malpas stated that the operation by Professor Leith Murray had been performed subsequent to the birth of the last child.

Dr. L. Strang read a short paper on

THE SURVIVAL OF BABIES AFTER CAESAREAN SECTION

Dr. Strang recalled that in a paper read to the Society by Bryan Williams in 1950 it was postulated that the operation of Caesarean section carries a special risk for the baby, a point also made by a number of authors in the United States. Furthermore a syndrome of respiratory distress terminating in death between 24 and 48 hours has been described and attributed to the operation: it has been called the "Caesarean section syndrome". Yet no similar syndrome had been encountered at the Princess Mary Maternity Hospital in Newcastle.

It therefore seemed to be of great importance to find out the truth of this matter, since a choice frequently exists as to the method of delivery; for example, in terminating a pregnancy complicated by severe toxaemia at a stage of gestation when surgical induction often failed. It was necessary, therefore, to be sure that section carried no extra hazard to the baby, and the present investigation had been undertaken to this end.

It seemed evident that no estimate of the role of operation in influencing survival was possible except in those operations undertaken where the baby was not already at risk from the effects of a prolonged labour or placenta praevia. None of those describing the "Caesarean section syndrome" had limited themselves to the elective operation. For example, Potter and Rosenbaum (1943) and Williams (1950) included cases where placenta praevia and rupture of the uterus had been indications for the operation.

Most published series of Caesarean section quoted neonatal death rates for all types of section. These rates varied between 2.5 per cent and 5 per cent, but necessarily included many cases where the scales were loaded against the baby before the operation. Marshall (1949), whose series was the largest, gave separate figures for cases classified as "elective" or "of favourable omen". There were 2.45 per cent neonatal deaths, not excluding premature babies and prematurity was associated with over half of the neonatal deaths. More recently Zarov (1952) had no neonatal deaths and only 1 stillbirth in 238 elective sections.

It seemed, continued Dr. Strang, that the only way to decide whether abdominal delivery was more dangerous for the baby than vaginal would be to compare a series of uncomplicated vaginal deliveries at term, with a concurrent statistically large series of Caesarean sections. Such a comparison was not available in the literature, but it was decided to see if some sort of answer could be derived from the records at the Princess Mary Maternity Hospital.

The case records of all Caesarean sections from 1946 to 1950 inclusive were therefore examined and divided into 3 groups:

(1) Those performed before labour or within a few hours of the onset of labour where a clear intent to perform a section was expressed in the antenatal record. This group was termed *elective*.
(2) Those performed for some emergency purpose such as foetal distress or placenta praevia, or as the termination of a trial of labour. This group was termed *emergency*.
(3) Those performed for a purpose which was not clear from the records, or which did not fall into one of the above groups. This group was termed *doubtful*.

Results. The foetal and neonatal loss was determined for each group (Table I).

It was at once apparent that the number of elective sections was not sufficient to permit a statistical comparison with a group of uncomplicated vaginal deliveries over the same period.

TABLE I
Foetal Mortality in Caesarean Section

	Elective	Emergency	Doubtful	Total sections
Number	179	267	7	453
Combined foetal and neonatal loss	12	35	—	47
	(6.7 per cent)	(13.1 per cent)		(10.1 per cent)
Stillbirths	3	19	—	22
	(1.7 per cent)	(7.2 per cent)		(4.6 per cent)
Neonatal deaths	9	16	—	25
	(5.0 per cent)	(5.9 per cent)		(5.5 per cent)

Stillbirths and neonatal deaths in the elective group were then examined. There were 3 stillbirths, but discussion of these was not pertinent. There were 9 neonatal deaths, and the paediatric case records and autopsy reports of these were studied. The causes of death were as recorded in Table II.

TABLE II
Causes of Neonatal Death following Elective Caesarean Section.

Extreme prematurity (less than 3½ pounds) ...	3
Extreme prematurity and tracheo-bronchial fistula	1
Gross congenital abnormality	2
Haemolytic disease	1
Massive pulmonary haemorrhage	1
Cause obscure	1
Total	9

The cause of death remained obscure in 1 baby delivered by section for contracted pelvis. The birth weight was 6 pounds 2 ounces and the baby breathed normally at birth, but was noted at 24 hours to be cold, cyanotic, and moaning. This persisted until death at 42 hours. At necropsy there was atelectasis and early bronchopneumonia. The bladder was enlarged, and there was some doubt as to whether there was an internal urethral orifice present, but this was not firmly established.

Dr. Strang concluded that all of the 9 neonatal deaths occurring after 179 elective sections were, except 1, clearly attributable to a cause unrelated to the operation and no case of "Caesarean section syndrome" had been seen.

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Discussion

The President said that it was important to know if the risk to the baby was increased by Caesarean section, and he thought that Dr. Strang's paper had been reassuring in this respect.

Mr. F. Stabler said that in Newcastle the "Caesarean section syndrome" had not been seen, largely due to the attention given to minor points in organization and technique. Even the shortest period of anoxia in the mother before section was harmful to the baby. This was one occasion upon which the surgeon must be prepared to wait for the anaesthetist, and the anaesthetic should be started no earlier than was absolutely necessary. Arrangements were made at the Princess Mary Maternity Hospital for a paediatrician to be in attendance at the theatre by day or night to take over the baby immediately after birth.

Professor T. N. A. Jeffcoate said that all had had the experience of losing a baby unexpectedly after a Caesarean section, or, for that matter, after a vaginal delivery. He had reported that Caesarean section gives rather a better outlook for premature babies in

toxaemic cases, but he thought it probable that the deaths had been transferred from the stillbirth to the neonatal column. He would like Dr. Strang's comments upon the 3 cases of stillbirths glossed over in his series. He agreed that the technique was very important and asked what type of anaesthesia was favoured in Newcastle.

Mr. B. Williams was satisfied that the "Caesarean section syndrome" did exist. A baby could be quite well at birth, and 1 hour later could be cyanotic, responding unsatisfactorily to treatment and dying within 24 to 48 hours. At postmortem examination a hyaline membrane might be demonstrated in the lungs and in 1 case massive pulmonary haemorrhage had been found. Browne and others claimed that the Caesarean section baby had a greater risk in starting life than the normally delivered baby. It has been suggested that aspiration of fluid from the stomach of the infant at birth would obviate any risk of the syndrome developing. The paediatrician must take stillbirths into consideration.

Dr. W. Calvert referred to Greenhill's figure of 5 per cent foetal mortality for Caesarean section and said that he had made a plea for the use of local anaesthesia at the Bicentenary Congress held at the Rotunda Hospital. He was now in favour of general anaesthesia with a competent anaesthetist, being of the opinion that if any form of premedication was given before local anaesthesia this might do more harm than a general anaesthetic. It should not be forgotten that typical tentorial tears could result from an attempt to deliver the head through too small an incision at Caesarean section.

Dr. Strang, in reply, said that the present practice was to give general anaesthesia, with awareness that anoxia and deep anaesthesia were harmful. If there was reason to believe that the airways were obstructed and the child too feeble to expel the plug of mucus, laryngoscopy and suction were practised, but the tube was not passed beyond the cords. A string of tenacious mucus over the glottis was sometimes responsible for respiratory obstruction, but in most cases the baby was allowed to rest with its head low in a cot while oxygen was administered. In some cases the child was put into an oxygen tent. He understood that 56 per cent of all premature babies who died had hyaline disease whether or not they had been delivered by Caesarean section. No case of direct cerebral damage had been encountered in his series.

Dr. R. F. Lawrence read a short paper on

VAGINAL DELIVERY AFTER CAESAREAN SECTION

(This article appears on page 237)

Discussion

The President did not agree that the dictum "once a Caesarean section, always a Caesarean section" could be justified. He recommended a middle course judging each case on its merits.

Dr. K. Baker stated that during the past 20 months 86 patients with a history of previous transverse lower segment Caesarean section had been delivered in Mill Road Maternity Hospital, Liverpool. The results in the labours subsequent to the sections were as follows:

Method of Delivery in 86 Women Previously Delivered by Caesarean Section

Mode of delivery	No. of cases	Maternal mortality	Foetal mortality
Elective repeat Caesarean sections	15 (17.45 per cent)	0	0
Trial labour—repeat Caesarean sections ..	9* (10.45 per cent)	0	0
Trial labour—vaginal delivery	62 (72.1 per cent)	0	2 (3.2 per cent)

* Including 1 case of ruptured uterus.

One patient had been delivered previously after a trial labour by a lower segment section on account of disproportion. On the second occasion after 6 hours in labour it became clear that the head was unable to pass through the brim, and abdominal delivery was performed. There was no supra-pubic tenderness and normal labour pains were present, but on operation the scar was found to have ruptured. This case illustrated the risk of vaginal delivery following Caesarean section, and unfortunately there was no method by which this risk could be assessed with certainty other than by a trial of labour. After delivery, however, immediate intra-uterine palpation had been performed in 54 of the 71 cases submitted to labour with the following results:

Direct Uterine palpation, 54 cases; Defective scars 6 cases

	Indication for previous section	Type of operation	Maturity	Site of incision
Case I	Placenta Praevia	Elective	28	Upper segment
Case II	Placenta Praevia	Elective	36	Upper segment
Case III	Postmaturity	Elective	43	Upper segment
Case IV	Contraction ring	After 6 hours in labour	40	Upper segment
Case V	Uterine inertia	After 36 hours in labour	39	Junction of upper and lower segments
Case VI	Placenta Praevia	Elective	37	Junction of upper and lower segments

In the remaining 47 cases the scar was intact and not lying in a depression. In 3 of these cases, however, there was a slight broadening of the scar on one or other angle. It would appear that the best guarantees against rupture of the scar in a subsequent labour were that greater attention should be paid to the closure of the ends of the incision and that the incision should be placed as low in the uterus as possible. If strict attention was paid to these two points at the primary operation, vaginal delivery in hospital after lower segment Caesarean section would appear to be a safe and sound obstetrical procedure.

Professor Farquhar Murray said that he agreed that a repeat Caesarean section was not necessary solely because a previous Caesarean had been carried out, especially when the original section had been performed for some condition other than disproportion. He advised, however, that a patient who had previously had a section should always be delivered in hospital in any subsequent pregnancy.

Dr. H. Doberman considered that if in a first inert labour terminated by section the cervix had reached two-thirds dilatation, the outlook was usually favourable for a subsequent vaginal delivery. In cases of arcuate uterus some patients had an easy and some a difficult labour following Caesarean section.

Dr. Lawrence was of the opinion that the patient should be told that a repeat Caesarean section was not always necessary.

Mr. F. J. Burke read a paper on

Metastasizing Hydatidiform Mole

Metastasizing mole, said Mr. Burke, rarely referred to in the literature today, was known and written about towards the end of the last century. At that time it was classified as chorionepithelioma and it is of interest that Marchand used cases of this type to prove that chorionepithelioma originated in trophoblast and not decidua. The innocent nature of this lesion had been emphasized by several authors, including Pick, who described the first case in 1897; but in some recent publications it appeared to be regarded as a type of chorionepithelioma.

In the present case, a bluish-black nodule, 1 inch in diameter, was found on the vaginal wall, posteriorly and to the left of the urethra, when a mole was being evacuated from the uterus. Another interesting finding in the case was a fresh 14–16-weeks foetus with some apparently normal placental tissue. The vaginal nodule was excised and sections showed typical giant hydatidiform villi under the vaginal mucosa. The Aschheim-Zondek test was positive in dilutions of 1/50 and 1/100, and 1 week later a second vaginal nodule was found. The uterus and appendages with a large cuff of vagina, which included the second nodule, were removed by the vaginal route. The uterine cavity was smooth and there were no lutein cysts in the ovaries. Sections of the uterus and ovaries showed no evidence of invasive mole and the second vaginal nodule consisted of degenerated choriomatous tissue. X-ray examination of the chest was negative. The Aschheim-Zondek test became negative 4 weeks after the initial operation and all subsequent tests were negative. Deep X-ray therapy was given and the patient made a good recovery. She had been seen from time to time during the past 9 years and had remained perfectly well.

Mr. Burke commented on the rarity of co-existing foetus and mole *in utero*, and a short review of the literature was given, but interest was mainly directed to the significance of the metastases. It was pointed out that several pathologists regarded the presence of villi in choriomatous tissue as evidence of a benign lesion. Mr. Burke had reviewed the literature of metastasizing mole and found a total of 16 cases, only 4 of which proved fatal; 2 of these had died from secondary haemorrhage, 1 from post-operative peritonitis, and the 4th had such extensive occlusion of the pulmonary circulation as to cause death by asphyxia. In none of these cases was there any evidence to show that a metastasizing mole was capable of progressive malignancy.

Discussion

The President said that he had a patient dying in his wards with well-formed villi in the recto-vaginal septum. This was surely a malignant condition.

Professor Farquhar Murray referred to a case in which he had found a plum-coloured deposit in the uterine cornu which was a broad ligament chorionepithelioma apparently growing from without inwards to the uterine wall.

Mr. E. Stacey was of the opinion that the patient dying with villi in the septum was possibly dying from chorionepithelioma, and that the villi were persistent evidence of the presence of an old metastasizing mole. The true chorionepithelioma was rare. He had had a case simulating an ectopic pregnancy which proved to be a chorionepithelioma and this patient had died of innumerable deposits including bony metastases. This patient had never been pregnant and the growth was similar to that which might be found in the male testicle.

Mr. Burke, in replying, said that the post-molar tissue after expression of the hydatidiform mole was not chorionepithelioma, although chorionepithelioma might follow later. The presence of villi indicated tissues which were well differentiated and therefore which tended to regress.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

October 1952

The President, Mr. P. Malpas, took the chair at a meeting of the North of England Obstetrical and Gynaecological Society, held in the School of Clinical Studies, Manchester, on Friday, 24th October, 1952.

Mr. O. Vaughan Jones described a case of

CRUSH FRACTURE OF THE DORSAL SPINE IN ECLAMPSIA

(This article appears on page 259)

The remainder of the meeting was devoted to a symposium on "Anaesthesia in Obstetrics".

Dr. J. Hargreaves read a paper on

GENERAL ANAESTHESIA IN MIDWIFERY

Dr. Hargreaves pointed out the importance of realizing that many cases were emergencies which meant that preparation for anaesthesia was minimal, and very often it was not possible to choose the anaesthetist so that the most suitable member of the team present frequently had to assume this responsibility. New anaesthetic agents, introduced for other types of surgery, were often unsuitable for midwifery, and there was a danger of these methods being used by inexperienced anaesthetists. The planned operation in midwifery where proper preparation was possible was often anaesthetized by trained anaesthetists when perhaps their skill was least needed.

At term the maternal respiration was embarrassed and overtaxed to supply the needs of the foetus and of the muscular efforts of labour. Any material reduction in oxygen intake whether due to inadequate ventilation or low oxygen pressure in the respired gases soon led to maternal embarrassment and eventually to foetal distress. Respiratory depression or obstruction should be carefully avoided. The intravenous barbiturates, being powerful respiratory depressants, were not very suitable in such circumstances, and in addition they predisposed to respiratory spasm.

There was a marked slowing of gastric activity in labour which amounted to stasis in many cases. perhaps the onset of labour stimulated the appetite or perhaps an adequate meal had some effect in influencing the onset of labour. Therefore a full or partly full stomach was often present and should always be suspected in midwifery anaesthetics. This naturally recommended spinal analgesia as an alternative to general anaesthesia. This subject was to be dealt with by another speaker, but he would say that, when it was used for abdominal operations in midwifery, safety depended upon keeping the level of analgesia sub-umbilical so that respiratory embarrassment due to intercostal paralysis was minimal, while inhalation of oxygen was given as a routine. When these precautions were not observed a serious degree of collapse might occur. The fact that this could be successfully treated by oxygen therapy supported the theory that the collapse was primarily due to respiratory insufficiency.

The ideal anaesthetic for routine procedures in midwifery would give a fairly slow induction and an absence of respiratory depression or tendency to spasm. Maintenance at a light level of anaesthesia should be possible and the level should be readily controlled. Finally, in heavier dosage, relaxation of the uterine muscle should occur. A fairly slow induction was desirable so that an opportunity was given for dealing with gastric distension. For instance, under ether a patient might vomit during induction, but this was an active muscular effort occurring while the laryngeal reflexes are present, and therefore safe provided the mask was removed to allow the vomitus to escape. During the same stage of anaesthesia a stomach tube could be introduced without serious risk of laryngeal spasm. Intravenous barbiturates on the other hand neither stimulated vomiting early nor permitted the passage of a stomach tube in light anaesthesia without the occurrence of laryngeal spasm. It was possible to maintain light ether anaesthesia without spasm; with intravenous barbiturates this was not so and in order to carry on smooth anaesthesia a deeper level was usually needed, with the dangers that passive vomiting due to relaxation of sphincters might occur, while the laryngeal reflex was sluggish or absent. The risk of depressing the foetal respiratory centre must be remembered. Intravenous barbiturates should be used in midwifery only for induction in doses not exceeding 0.25 g., and should usually be reserved for patients who are nervous of a face mask. The drugs which relaxed the uterus were ether and chloroform. Finally the ideal anaesthetic should be non-toxic. Ether was therefore to be preferred to chloroform except when fire danger was insurmountable. Ether was toxic in heavy dosage, but as such dosage was required in midwifery only for internal versions, and then only for short periods, its other advantages outweighed the disadvantages. In light dosage, however, this drug was safe and reliable.

The safest method of using ether was by an open mask. Firstly, because the oxygen pressure was constant, and ill-fitting and absorbent masks were better receptacles for vomitus than the rubber face masks of a gas-oxygen machine. If a gas-oxygen machine were used for giving gas, oxygen and ether in midwifery the oxygen flow should never be below 10 per cent; the mask should not be secured by a harness but should be held in position by the anaesthetist, who should be ready to remove it if there was any sign of vomiting. Whenever anaesthesia was required in midwifery a large stomach tube, a laryngoscope and Magill's tubes should be at hand. Endotracheal intubation was rarely needed as the depths of anaesthesia would not be deep enough to allow this to be done safely. Collapse, haemorrhage or deep anaesthesia might at any time make this procedure advisable as a safeguard against aspiration.

When general anaesthesia was required for Caesarean section a light ether anaesthetic was often suitable but with foetal distress or maternal disease there were certainly advantages in using small doses of relaxant drugs with thiopentone and/or ether. The maternal diseases most commonly seen were metabolic or cardiovascular. In the former group anaesthesia could be maintained by gas-oxygen and cyclopropane and in

the latter by gas-oxygen ether. A small dose of tubarine not exceeding 15 mg. was given merely to prevent spasm and to allow smooth anaesthesia at a light level, while leaving the patient with effective respiratory movement and laryngeal reflex. In small doses the oesophageal sphincters were not relaxed and prostigmine was not needed after operation to restore muscle tone, but might stimulate dangerous vomiting. The safe dose of relaxant for Caesarean section should never require the use of prostigmine. The injection of tubarine was followed by a small dose of thiopentone, the total amount used being less than 0.25 g. Anaesthesia was maintained at a light level, cyclopropane or ether being given with gas and oxygen either in the closed or continuous flow circuit. The airway was by the natural air passages whenever possible. A pharyngeal airway was used if necessary, and stomach tube and intratracheal tubes were kept handy, though he had never had to use the latter for this type of case. Foetal respiration was usually spontaneous and vigorous. It was worth while having a small laryngoscope and Magill's tubes sizes 00–1 for the very rare case when insufflation of the foetal lungs might be of value.

Passing a stomach tube before anaesthesia for midwifery could be defended as a step to safer anaesthesia. Being unpleasant for the patient, it should only be done when the anaesthetist was not confident of being able to maintain a light and smooth anaesthetic. But it was obviously preferable to running an unnecessary risk. However, a full stomach was not easily emptied and a sense of false security might be more dangerous than a known risk.

Pre-medication was most important. Pre-operative sedatives were best avoided and, if specially indicated, should be given well in advance or else given intravenously so that the maximum effect was seen before induction of anaesthesia. The best routine agent was atrophine gr. 1/100. A careful record of sedatives given in the preceding 24 hours should be available so that the combined effect of sedatives and anaesthetic could be allowed for in the choice and dosage of anaesthetics; for embarrassing respiratory depression might occur with thiopentone when other barbiturates had been given to the patient in the pre-operative period.

Finally Dr. Hargreaves stressed the importance to the anaesthetist of being allowed to feel that he was a member of the obstetrical team, for when a young anaesthetist got into difficulties with obstetrical cases it was often due to over-anxiety to give quiet operating conditions.

Dr. H. Roberts read a paper on

THE MATERNAL RISKS OF LOW SPINAL ANALGESIA

Dr. Roberts said that his comments were based on an analysis of 3,230 cases of saddle-block spinal analgesia carried out at Walton Hospital, Liverpool, in the 12-year period January 1936 to December 1947.

Technique. With the patient sitting up on the edge of the bed resting her folded arms on her knees, the subarachnoid space was entered through the 4th or 5th lumbar interspace. Fifty milligrams of sterile crystalline " planocaine " (Procaine) were mixed with a small volume of C.S.F. and injected slowly. The patient remained sitting up for a further 5 minutes to allow the planocaine to fix.

Dr. Roberts emphasized that in saddle block the risks of abdominal block, necessary for Caesarean section, were avoided. Thus hypotension, pallor, restlessness and vomiting were absent as well as the danger of ascending intercostal paralysis.

Type of Case. Cases of toxaemia and with gross associated diseases were included as well as normal labour. The only contra-indications were recent haemorrhage, shock and intra-uterine manipulations requiring abdominal relaxation.

Type of Operation. Forceps delivery was undertaken in 1,559 cases, breech delivery in 328 cases, embryotomy in 21 cases, surgical induction of labour by stomach tube or bougies in 13 cases; perineal repair in 1,398 cases (all before 1943); and internal version in 1 case.

For breech delivery the analgesia was administered when the buttocks distended the vulva. Throughout the delivery the co-operation of the conscious patient was available—a great asset.

The number of embryotomies, indicating the number of difficult emergency cases encountered, was a reminder that this series of cases was dealt with some time ago.

One of the disadvantages of low spinal, said Dr. Roberts, was that it did not relax the abdominal and uterine musculature, so that manual rotation of the head might be difficult, and indeed manual rotation in deep transverse arrest was successful in only 63 per cent.

In the forceps series postpartum haemorrhage of over 20 ounces occurred in 103 cases, an incidence of 6.6 per cent, an average figure for those years. Manual removal of the placenta was necessary in 23 cases (1.5 per cent). In addition, there was 1 case of acute puerperal inversion of the uterus. These figures suggested that saddle block, unlike abdominal block, did not enhance uterine action in the third stage.

Maternal Deaths. There were 14 deaths within 42 days of delivery among the 3,230 women. Nine women died more than 24 hours after the spinal analgesia and from causes unrelated to it. The 5 deaths which occurred within 24 hours required closer scrutiny.

Two were cases of obstructed labour due to an impacted deep transverse arrest and locked twins respectively, and the exact diagnosis was only made at the examination under spinal. There was no shock present when supplementary ether anaesthesia was induced for the difficult and prolonged manipulations undertaken. One of these 2 women also had a manual removal of the placenta performed for third stage bleeding. These deaths occurred 4 and 8½ hours respectively after spinal analgesia was induced.

Two other women who died were delivered by forceps under spinal analgesia. In both the placenta

was retained for over 2 hours and there was considerable haemorrhage leading to the gradual onset of shock. There was no shock immediately after delivery and the spinal analgesia had worn off completely when manual removal of the placenta was performed under open ether. Both these cases occurred before the days of organized transfusion services. Death occurred 4 and 7½ hours respectively after delivery.

The remaining death was due to eclampsia, as proved by postmortem. Low forceps delivery had been carried out under low spinal analgesia at a time when she was too ill for any other form of anaesthesia, and she died 9 hours later.

In all these 5 cases there was adequate obstetrical cause for death and, although it was impossible to exonerate the spinal completely, there was no evidence to suggest that it was a contributory factor.

Complications. Post-spinal headache occurred in 613 women (19 per cent). The longest duration of headache was 17 days, and it lasted longer than 1 day in 7.7 per cent. Lumbar puncture was performed in 27 severe and persistent cases. The intrathecal pressure was low in 17 cases, raised in 5, and there was blood intimately mixed with the C.S.F. in 5 more. Cultures of the C.S.F. remained sterile in all, except for 1 case of pneumococcal meningitis.

Temporary diplopia due to 6th nerve palsy occurred in 5 cases.

Retention of urine occurred in 273 women (8.5 per cent), but it might not always have been due to the spinal. In more than a quarter of the women retention persisted longer than 1 day, the longest duration being 16 days.

The only other complications were broken needle (1 case) and septic meningitis (1 case); fortunately in both the outcome was favourable.

Dr. Roberts concluded that saddle-block spinal analgesia was free from serious risk to maternal life, but had advantages and disadvantages which many might consider cancelled each other out.

Dr. R. W. Burslem read a paper on

ANALGESIA WITH TRICHLORETHYLENE AND PETHIDINE HYDROCHLORIDE

An investigation was carried out on 1,130 women in labour to see whether a combination of these drugs formed an adequate method for general use in hospital obstetrics: 694 (or 52.4 per cent) of the patients were primigravidae, and the cases were unselected. Three hundred and two of the patients were unbooked cases; but the majority of the remaining cases had been given a few minutes instruction in the antenatal clinic on the use of the Trilene inhaler.

In general, the inhalational analgesics such as nitrous oxide and air or Trilene were unsuitable for early labour, and they were most useful towards the end of labour when the pain was at its worst. Pethidine was used effectively as an analgesic of early labour. Its effect on the pain threshold was determined in 3 subjects by the method which Hardy, Wolff and Goodell (1940) used to investigate the analgesic properties of morphine derivatives.

Briefly, the light from a 1,000-watt lamp was focused by a condensing lens through a fixed aperture on to the blackened forehead of the subjects. The skin was blackened with indian ink in order to ensure total absorption of the radiation regardless of skin pigmentation. The pain producing stimulus was purely thermal. The intensity of the radiation was controlled by means of a rheostat. In front of the lamp was mounted an automatic shutter which allowed the radiation to pass for exactly 3 seconds, so that heating of the skin was local and conduction from the edges of the aperture could be ignored; therefore the temperature changes in the exposed area were assumed to be uniform.

After the skin had been irradiated for 3 seconds the subject reported what she felt. If there was no pain, there was a wait of a few minutes and then the intensity of the light was increased and the test repeated. This went on until the subject felt pain at the end of the exposure. The sensation was one of heat, first "pricking" and finally "stabbing" in quality. When this had been reached a radiometer was placed in the position occupied formerly by the subject's forehead so that a measure of heat intensity could be made.

The test was repeated after intramuscular injection of 100 mg. of Pethidine. Readings were taken at 15-minute intervals for 3 hours.

A composite graph of the results showed that the thermal pain threshold was raised at its maximum 15.5 per cent and this was reached 45 minutes after the injection of 100 mg. of Pethidine. Return to the base line occurred on the average in just over 2½ hours.

Classification of Patients

The patients in this series fell into three arbitrary working groups.

Group 1. Women in early labour with the cervix no more than 3-fingers dilated and often less than this.

Group 2. Women about "mid-labour" with a minimum cervical dilatation of 3 fingers and a maximum of three-quarters dilatation.

Group 3. "Late-labour"—beyond three-quarters dilatation or in the second stage of labour.

Using this grading numbers were:

	No. of cases	Per cent of total
Group 1	810	71.68
Group 2	159	14.12
Group 3	161	14.20
Total	1130	100.00

Method of Analgesia

Group 1. The initial medication was Pethidine hydrochloride, 100 mg. intramuscularly as soon as the patient was disturbed by pain. A further 100 mg. was given when the effect of the first dose was waning, usually 3–4 hours later.

The analgesic effect of Pethidine seemed to be more prolonged on uterine pain than on thermal pain produced in the experiment, as in the latter the analgesia was almost gone 2½ hours after the Pethidine as compared with 3–4 hours in labour.

Trilene, self-administered by the patient from a Woodfield-Davies inhaler, was begun as soon as the effect of the second dose of Pethidine required reinforcement—usually when the os was about three-quarters dilated.

Group 2. One hundred and fifty milligrams of Pethidine was given on admission, and the inhalation of Trilene was started at the same time. If necessary, and if the os was not yet fully dilated, a further 100 mg. of Pethidine was given when required, usually about 4 hours after the first dose.

Group 3. Trilene was begun at once and, if necessary and progress was slow, 100 mg. of Pethidine was given slowly intravenously.

Grading. Analgesia was graded as good, satisfactory, poor or failure.

"Good" analgesia meant that the pain appeared to be greatly relieved, and the patient agreed that this was so both during labour and the following day.

"Satisfactory" analgesia meant that the labour pains were still uncomfortable but that there was partial relief, and also that there was an observable contrast in the patient's behaviour before and after analgesia.

"Poor" analgesia was when the patient had little relief from her pains but felt that the analgesia was of some help.

"Failure" occurred when it was obvious that there was no pain relief.

Results were as follows:

(1)	Good	641	56.7 per cent
(2)	Satisfactory	347	30.7 per cent
(3)	Poor	90	8.0 per cent
(4)	Failure	52	4.6 per cent

Cripps, Hall and Haultain (1944), working with Pethidine alone and using a similar classification of the analgesia produced, obtained good or satisfactory analgesia in 78.4 per cent. This contrasted with 87.4 per cent in this series. It was reasonable to assume that the addition of Trilene caused the increased rate of adequate analgesia.

In reviewing the 142 cases in the "poor" and "failure" groups, the method by which the analgesia was applied seems to have been deficient in 109 of the patients, and the analgesic drugs themselves were deficient in the remaining 33.

Dosage of Pethidine and Trilene. The 694 primigravidae received a mean dose of 288 mg. of Pethidine, the limits being 100 and 500 mg. respectively. The mean dose in multigravidae was 252 mg. but the highest individual dose was 450 mg. of Pethidine, and the lowest was 100 mg.

Of Trilene, the mean amount used was 32 ml. in primigravidae and 20 ml. in multigravidae. The highest dose was 42 ml. Average consumption was 6.2 ml. per hour in primigravidae and 5.8 ml. per hour in multigravidae. The longest administration was 10¼ hours, and the average duration of administration 4.3 hours.

Effect of Analgesia on Uterine Contractions

Labour was not prolonged compared with similar unselected series of cases who had received either gas and air, potassium bromide and chloral mixtures, or both.

The Lorand (1936) type of tocography on 25 random cases before and during Pethidine-Trilene analgesia showed no demonstrable difference in the amplitude or frequency of the contractions. However, this type of instrument was of low sensitivity and therefore this evidence must be treated with suspicion.

The forceps rate was 6.2 per cent, representing 70 forceps extractions. By comparison, in a large series of cases (nearly 4,000) collected b the Royal College of Obstetricians and Gynaecologists of gas-and-air analgesia, the forceps extraction rate was 6.6 per cent.

Postpartum haemorrhage. There were 11 cases of postpartum haemorrhage or third-stage bleeding. This rate of 0.96 per cent compared fairly well with most reported series, but was nevertheless not good.

Blood loss in general. There were 11 manual removals of the placenta, and in 4 of these there was an associated postpartum haemorrhage.

In the whole series of cases there were no maternal deaths from any cause.

Effects of Analgesia on the Child

One thousand, one hundred and sixty-one infants were delivered, as there were 31 cases of twins. The state of the infant at birth was assessed according to Schumann's classification (1944) which is:

Grade (*a*): The infant breathes spontaneously at birth or immediately after it and no resuscitation is required.

Grade (*b*): The infant breathes within 2 minutes of birth, and no resuscitation beyond aspiration of mucus is necessary.

Grade (*c*): More than 2 minutes elapses before respiration begins. Respiratory stimulants are usually necessary.

Grade (*d*): Stillbirths.

The results were:

Classification	No. of infants	Percentage of total
(*a*) Active infants	1036	89.3
(*b*) Slightly slow	69	5.9
(*c*) Slow	20	1.7
(*d*) Stillbirths	36	3.1
Total	1161	100.0

Of the 20 "slow" infants in Grade (*c*), 14 were after operative delivery when a general anaesthetic was used, 3 were premature infants and 3 were apparently straightforward spontaneous deliveries of mature

infants in which it is quite possible that the analgesia solely was responsible for their condition. Two of the 36 stillbirths (all of whom were autopsied) were due to asphyxia. In the remaining 34 cases other pathological lesions were present, which had no apparent connexion with analgesia or asphyxia.

Blood gas analysis. The arterial and venous oxygen contents in cord blood of 6 newly born infants were measured immediately after birth. These infants were delivered normally, and their mothers had been given Pethidine and Trilene analgesia. Similar analyses were performed on 4 babies whose mothers had had no analgesia. The analyses were by the Peters and Van Slyke (1932) method.

The average volume per cent of oxygen in the umbilical vein was 12.5 in the text as compared with 13 in the controls; for the umbilical artery the figures were 3.3 and 3.4 respectively.

Neonatal death rate. There were 25 neonatal deaths. Eighteen of them occurred within the first 7 days of life; 5 of these were, at postmortem, shown to be due to atelectasis or purely asphyxial death. Fourteen of the infants were premature in this group.

In conclusion, Dr. Burslem pointed out that it was difficult to obtain a complete picture of the effect of any method of analgesia on mother and child and therefore conclusions should be drawn with caution. Both Pethidine and Trichlorethylene had, however, stood the test of time, and the combination of the two appeared the most satisfactory method at present available for general use in midwifery departments of hospitals.

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Discussion

Professor A. M. Claye pointed out that the occasional anaesthetist was inevitably concerned in obstetrics, and therefore the student must be taught simple methods of anaesthesia, however complex the technique of the specialist anaesthetist might become. In addition both the student and midwife needed instruction in analgesia methods such as that outlined by Dr. Burslem. A foolproof Trilene machine would soon be devised.

Dr. O. Bark, speaking as a general practitioner who was perforce an occasional obstetrician and an occasional anaesthetist, proclaimed the merits of open ether, while Dr. Cuthbert, an anaesthetist, considered chloroform suitable for domiciliary midwifery and caudal analgesia useful in hospital practice.

Professor C. Scott Russell contemplated the possibility of sub-clinical meningitis or delayed neurological symptoms after spinal analgesia. He preferred local analgesia, but, if a general anaesthesia were employed, intravenous ergometrine should be given routinely at the close of the second stage of labour.

Mr. C. H. Walsh was another protagonist of local analgesia. General anaesthesia involved the risk of inhalation of vomit, and, while the problem of the delayed emptying of the stomach in labour had not been completely solved, it would help if women in labour were allowed clear fluids only by mouth.

Dr. Hunter, an anaesthetist, advocated that students should be instructed in obstetric analgesia and anaesthesia in an obstetrical unit. He found that gas-and-air analgesia gave relief in 80 per cent of women in labour and he doubted if that figure could be exceeded by the use of any drug at all.

Dr. G. J. Rees said that an endotracheal tube would prevent the inhalation of vomit. The liberal use of relaxants, which did not cross the placenta, would allow the use of smaller doses of anaesthetic drugs which do cross.

Mr. C. M. Marshall deplored that inadequate attention had been paid to general anaesthesia as a cause of maternal death. In the Liverpool Maternity Hospital there had been at least 8 deaths due to inhalation anaesthesia in 17 years. In 6 of these 8 the cause of death was inhalation of vomit, which in the U.S.A. had been stated to cause about 2 per cent of the total maternal mortality.

Other speakers differed on the efficacy of emptying the stomach by tube before anaesthesia: and also on the effect of relaxants on the ease or difficulty with which the foetus could be extracted at Caesarean section.

The President, winding up the discussion, doubted whether what had been said had changed anyone's convictions.

NEWCASTLE UPON TYNE OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

DECEMBER 1952

A meeting of the Newcastle upon Tyne Obstetrical and Gynaecological Society was held in the Newcastle General Hospital on 15th December, 1952. The President, Mr. Frank Stabler, was in the chair.

Mr. A. Hart described a case of

COMPOUND PRESENTATION

Mrs. E. T., aged 30 years, a primigravida, was seen by Mr. Hart for the first time on 27th August, 1952, when he found a pregnancy of about 24 weeks.

The pelvis was normal. She attended the Antenatal Clinic again on the 22nd October when she gave a history of the membranes having ruptured about 10 days previously and she was draining liquor all the time—no labour pains.

On examination he found a vertex presentation with the head at the brim; foetal heart heard. She was draining liquor; the cervix was not dilated. She was admitted to hospital on the same day. Liquor continued to drain and on the 2nd November labour started with very strong contractions. On examination he found the presentation still a vertex, but through the cervix which was dilated to 2 fingers a prolapsed cord and prolapsed foot were felt. The cord was pulsating and the presenting part was not engaged. There was hardly any liquor in the uterine cavity and the uterus was moulded tightly round the foetal body so that an internal version or even a reposition of the prolapsed parts was impossible.

Delivery by Caesarean section was decided upon and a lower segment type of operation was performed. A transverse incision was made and it was found that, apart from the prolapsed foot and cord, one arm was also prolapsed. The delivery was accomplished with some difficulty and a living child of 4 pounds 11 ounces was delivered. The baby had a tendency to lie doubled up during the first 2 to 3 days and an impression of the head on the lower parts of both legs was visible. This subsided after 3 to 4 days. Mother and infant were discharged on the 14th day in a satisfactory condition.

Discussion

Several speakers felt that it would have been preferable in this case to perform an upper segment Caesarean section. One member of the Society suggested that the original transverse incision in the lower uterine segment might have been converted to a T-shaped incision by means of a vertical incision up into the upper segment. Mr. Stabler disagreed with this suggestion as he had always been of the opinion that this type of incision passing from lower segment to upper segment was particularly liable to rupture in a subsequent pregnancy.

Dr. J. K. Russell read a paper on

AETIOLOGICAL FACTORS IN MALE SUBFERTILITY

Dr. Russell began by drawing attention to the inadequacy of treatment in established cases of male subfertility. It was therefore important, he felt, to study the aetiology of subfertility in an attempt to prevent the occurrence of the condition.

Dr. Russell compared 2 groups of men—100 fertile men in Group A, men whose wives had had repeated pregnancies at short intervals, and 120 subfertile men with poor quality semen whose wives had had no children.

Dr. Russell found no difference in the physique or nutritional states of these 2 groups of men, and concluded from this that nutrition was not closely related to fertility in the male. This view, he felt, was borne out by the large families which exist in the 'poorer' quarters of our cities.

The main differences between the 2 groups of men lay in the incidence of venereal diseases and varicocele. Such conditions as cryptorchidism, local injury to the testes and operation on the testes did not appear to be frequent causes of subfertility in the male.

In over half of the cases of subfertility, however, Dr. Russell could find no obvious aetiological factor. Dr. Russell referred to the work of several authorities who had studied this problem amongst cattle. So far as animals were concerned it seemed clear that genetic and environmental factors were important causes of subfertility.

Dr. Russell suggested that man's environment is changing so quickly that it may be adversely affecting his physiology. It seemed reasonable to suggest that among the group of men whose subfertility was unexplained environmental and genetic factors must be considered.

Dr. Russell suggested that further investigative work was required into the effect of environment and heredity upon fertility in the male.

Discussion

Mr. Stabler pointed out that varicocele is essentially a condition affecting younger men and tends to disappear after marriage. He suggested that the men with larger families were likely to be older and therefore less likely to suffer from this condition.

Mr. Linton Snaith expressed his interest in this approach to the subject and was interested to learn more of the environmental factors which were known to affect adversely fertility in cattle. Dr. Russell agreed with Mr. Stabler that fertile men were on the average 3 and 4 years older than the subfertile but he did not believe that the difference in age accounted entirely for the greater incidence of varicocele in the younger men.

So far as cattle were concerned the main environmental factors were considered to be infection and diet.

Dr. G. T. Johnson read a paper on

EXPERIENCES WITH CONTINUOUS CAUDAL ANAESTHESIA IN ABNORMAL OBSTETRIC PRACTICE

He began by referring to a paper on caudal analgesia presented in Newcastle upon Tyne in 1949 by Professor Hingson of Baltimore. In this, the pain involved in parturition had been vividly assessed, and the means whereby it could be completely relieved by caudal analgesia described and illustrated in detail.

Although the underlying principles of caudal analgesia were well established, Hingson and his colleagues were largely responsible for the modified continuous technique advocated by them. This method was endorsed with minor variations, but it was suggested that caudal analgesia seemed unlikely to achieve widespread popularity, in its present form, as a

primary measure for relieving the pains of labour, when reasonably satisfactory analgesia could be obtained by simpler means.

For this reason therefore there was no intention to discuss caudal analgesia from this aspect, but instead to submit the method as a therapeutic measure in the management of certain types of obstetric problem, and to present a report of experiences at the Newcastle General Hospital during the previous 3 years.

Caudal analgesia was submitted as a basically simple procedure, which involved blocking the sacral plexus with metycaine solution, and extending the level of analgesia upwards, in the extradural space, to include the sensory posterior root ganglia of the lumbo-dorsal region, and the lumbar sympathetic chain. A description of the anatomical and physiological considerations involved in caudal analgesia was presented, which was based on Hingson's conception of the pelvic nerve supply, an unproven thesis, which seems well borne out by caudal analgesia. It was pointed out that the sacral plexus lay below and external to the meninges in the confines of the sacral canal, and was a mixed plexus which supplied both motor and sensory nerves to the pelvic floor and perineum, with visceral parasympathetic nerves of both motor and sensory origin to the lower uterine segment and cervix. Part of the aim of caudal analgesia was to block the sacral plexus in its entirety, to allow the painless delivery of a foetus through a paralysed and insensitive birth canal and cervix.

Turning to the fundus, this like the cervix possessed a double visceral autonomic nerve supply, with both sensory and motor connections, but these fibres were relayed to the spinal cord in the lumbar sympathetic chain. The uterine sensory connections entered the cord in the region of the 10th dorsal segment, and the motor connections at the 5th. The latter were antagonized by the parasympathetic connections to the lower uterine segment and cervix which originated in the sacral plexus. It was pointed out that blocking the sacral plexus of the labouring patient by local anaesthesia not only paralysed the cervical and pelvic musculature, but it removed the parasympathetic opponents of fundal action in addition, and enhanced uterine action should be expected. The complete aim of caudal analgesia in parturition was to extend the level of analgesia upwards outside the meninges to the level of the 10th dorsal segment, to produce painless fundal action, with intact motor connections from the 5th dorsal segment higher up, thus allowing unopposed and painless fundal action to be exerted upon a paralysed lower uterine segment and cervix. This principle was employed therapeutically in the management of a series of cervical dystocia and uterine inertia, in an endeavour to accelerate the whole process of labour.

There were certain side effects of caudal analgesia which were considered, of which bladder paralysis was the most important. This required catheterization during the course of caudal block, and for several hours afterwards to prevent dangerous distension.

Reference was also made to the pelvic and lower limb vasculature, the sympathetic connections of which were blocked simultaneously to produce vasodilatation, and consequent lowering of systemic blood-pressure. This required careful blood-pressure observations throughout caudal analgesia, and suggested 2 further therapeutic applications of the method, namely, the lowering of uncontrollable hypertensive crises arising in pre-eclampsia and eclampsia and a possible means of enhancing the maternal blood supply to the placenta, when foetal distress supervenes from suspected placental insufficiency.

The obstetric complications which had been subjected to caudal analgesia in the series discussed included the following: uterine inertia, cervical dystocia, severe and otherwise uncontrollable hypertensive crises of pre-eclampsia and eclampsia, maternal distress, foetal distress, and the occasional patient with cardiac disease who might benefit from a completely painless labour. At this point a table was shown enumerating the various numbers of cases treated in these different groups.

A detailed description of the technique of caudal analgesia followed, illustrated by a series of coloured lantern slides. The needle method was adopted in preference to the catheter method, and it was stated that the subsequent management of cases, after the satisfactory establishment of analgesia, was continued by a sister who was thoroughly conversant with the technique. Reference was also made to the various contra-indications to the method as enumerated by Hingson, and special emphasis was placed upon the avoidance of the technique when there was any evidence of cephalo-pelvic disproportion.

The paper concluded with a report of the results obtained in the various types of obstetric problems enumerated previously, with special emphasis on prolonged labour from uterine inertia or cervical dystocia. Seventy-four cases of this latter type were subjected to the method, when labour had reached the 48-hour period. Analgesia was preceded by a careful vaginal examination to assess the state of the cervix and its degree of dilatation, and a second vaginal examination followed after 6 hours of satisfactory anaesthesia. As a result of this second examination progress was assessed and patients were placed into one of three categories. The first category comprised only of those with completely dilated cervices, who were successfully delivered by forceps. The second category included those who showed progressing cervical dilatation, and were subsequently delivered by forceps after a further period of analgesia of 3–4 hours duration. The third category comprised those patients who showed no response at all to caudal analgesia, and were therefore subjected to Caesarean section without further delay. Tables were shown to illustrate the very considerable improvement which resulted in the prospects for the foetus when this technique was adopted, the foetal mortality falling from 12.9 per cent in 1948, before the method was adopted in Newcastle General Hospital, to 1.4 per cent in recent years. The improved results were attributed to the adoption of positive line treatment

for the problem of prolonged labour. The method accelerated the progress of labour in many cases or, alternatively, resulted in earlier Caesarean section than might otherwise have been employed in those cases which did not respond.

The paper concluded with a plea for wider interest in continuous caudal analgesia in obstetric practice, especially in the management of prolonged labour. Experience so far had more than justified the requisite patience to master the technique and, bearing in mind the limitations of caudal analgesia, it had proved a most valuable addition to the obstetrician's armamentarium. As far as prolonged labour was concerned, the method seemed indicated when Caesarean section might be otherwise seriously considered as the only satisfactory solution. It was submitted that by its use many patients would achieve safe vaginal delivery, and be spared abdominal operation; nevertheless the outcome of a successful Caesarean section, in those cases which did not respond, would be in no way jeopardized.

Discussion

In the subsequent discussion the President congratulated the speaker on his paper and said that the illustrations shown gave those present a clear understanding of the present principles involved in both the technique and the management of patients by continuous caudal analgesia. The viewpoint that the method might have something to offer in the management of certain specific obstetric problems seemed a reasonable one, instead of its wholesale employment simply as a pain relieving measure, as advocated previously. Mr. Arthur endorsed these remarks, and added that he regarded the method as an important advance in obstetric technique, which relieved the obstetrician of much anxiety in the management of prolonged labour.

Members of the Society were particularly interested to hear the personal experiences of one of its members who had been subjected to caudal analgesia in the management of a prolonged labour.

BOOK REVIEW

"Recent Advances in Obstetrics and Gynaecology." By ALECK W. BOURNE and LESLIE H. WILLIAMS. Eighth edition. J. & A. Churchill, Ltd., London, 1953. Pp. viii + 339, illustrations 92; price 27*s.* 6*d.*

THE pace of progress in the science and art of obstetrics and gynaecology may be measured by the rapidly succeeding editions of this admirable book. Although it is only five years since the appearance of the seventh edition, in the preparation of this new edition it has been found necessary to scrap five and to add three new chapters.

From its first appearance under Mr. Bourne's authorship nearly thirty years ago *Recent Advances* has been more than a mere compilation of current literature. Whilst exercising a wise judgment in the assembling for the reader of the most important developments in the specialty it has at the same time brought to bear on these developments a rare critical and judicial discernment. These features are again well exemplified in this new edition. Thus the first chapter on "Nutrition of the Pregnant Woman," marshals all the most important new knowledge on this subject and succeeds at the same time in satisfying the reader that some of the claims advanced by enthusiastic workers rest on a very insecure basis. The chapter on "Cancer of the Cervix Uteri" includes an assessment of the work of American surgeons on the extended abdominal extirpation in cases which have advanced beyond the scope of ordinary surgery. In an excellent chapter on "Stress Incontinence" the authors have a valuable section on the sling operations and, whilst pointing to their advantages in selected cases, indicate that even in expert hands "some very unpleasant complications have arisen". They issue the caveat: "One must insist that this operation may be done only by operators who have been adequately instructed in the details of the operative technique. And even these operators must remember that they are performing a potentially dangerous operation and one in which dreadful consequences may follow if the straps are under undue tension."

Dr. E. Rohan Williams writes the chapter on "The Radiological Study of the Obstetric Pelvis, Foetal-Pelvic Proportions and of the Placental Site" and Dr. W. M. Levitt that on "X-Ray Therapy in Gynaecology".

This book has a wide range of usefulness—to the medical student, the general practitioner, and to the specialist at all stages of his career.

REVIEW OF CURRENT LITERATURE

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OBSTETRICS

1. **A Statistical Study for the Years 1946–50.** (Estudio estadtistico de la labor realizada durante el lustro 1946–50.)

By J. M. GUISADO INIGUEZ. *Rev. espan. Obstet. Ginec.*, **11**, 434–442, Nov.-Dec. 1952.

This survey is interesting because of the many differences which it shows in relation to a similar survey in Britain. It deals with the University Clinic of Obstetrics and Gynaecology under the direction of Professor Luis Recasens.

In the section which deals with operations one notes particularly the performance of 240 appendicectomies. Total hysterectomy was carried out 37 times and sub-total hysterectomy was performed 165 times for inflammation of the adnexa. Furthermore, salpingo-oöphorectomy was the operation of choice in 72 cases of tubal inflammation. This suggests a more radical approach to inflammation of the adnexa than is practised in this country. For retroversion of the uterus 98 Baldy and 16 Alexander-Adams operations were performed. There is no mention of the performance of Gilliam's operation, which is considered the best procedure in Britain.

Although anterior and posterior colpo-perineorrhaphy was performed 113 times, one notices that the interposition operation of Schauta-Wertheim was the method used in 107 cases, which again shows a marked divergence from British practice. Chronic cervicitis, which receives so much attention in Britain, was conspicuous by its almost complete absence.

[In the section dealing with dystocia I was surprised to note the performance of 12 basiotripsies, 7 decapitations, and 8 embryotomies, making a total of 27 destructive operations in all, whereas only 31 Caesarean sections were performed during the same period.]

D. G. Wilson Clyne

PREGNANCY

NORMAL

2. **The Histidinuria Pregnancy Diagnosis Test.**

By H. HANDOVSKY, M. THIERY, and R. PROVOOST. *Gynaecologia, Basle*, **134**, 401–412, Dec. 1952, 5 tables, 1 fig., 86 refs.

The authors claim to have devised a practical chemical pregnancy diagnosis test. This is a modification of the histidinuria test of Kapeller-Adler.

The technical details of the method are given in full.

The test has been carried out on 411 patients. In 127 non-pregnant sexually mature women, 126 presented a negative reaction. False positives were repeatedly found in genital malignancy. Positive results were also obtained in non-pregnant women with certain diseases, such as pulmonary tuberculosis, diffuse pelvic tuberculosis, diabetes and Cushing's syndrome.

In 172 healthy pregnant women, 168 (97.7 per cent) positive reactions were obtained. Two pregnant women with pyelonephritis gave negative results which became positive after the disease was cured.

In 28 cases the histidinuria test and the Friedman-Brouha test were performed simultaneously. The tests gave similar results.

It is concluded that the test compares favourably with biological tests for pregnancy, though it is a little less accurate. The apparatus required is not elaborate.

[There is an error in the authors' summary, 3rd paragraph. The figure 99.7 per cent should read 97.7 per cent if the figures are given correctly.]

Josephine Barnes

ABNORMAL

3. **Filtration Resorption and Excretion of Protein by the Kidney.**

By L. J. RATHER, *Medicine*, **31**, 357–380. Dec. 1952. 96 refs.

The "classical" thesis of renal function is that the renal glomerulus forms a protein-free filtrate. This review summarizes the evidence for the view that the glomerular filtrate normally contains concentrations of proteins which are related to the plasma levels of these substances even though they be of high molecular weight. Under normal circumstances the protein in the filtrate is reabsorbed by the renal tubules, probably being hydrolysed during this process by the enzyme systems in the mitochondria. In a normal man 27 g. of protein a day may be filtered through the glomeruli but the urine will contain only 160 mg. per litre. Albuminuria according to this concept is an evidence of overloading of the tubular reabsorptive capacity for protein rather than to increased glomerular permeability produced by noxious agents. This overloading may be due to increased plasma protein levels or diminished tubular capacity. Endocrines influence the protein reabsorptive mechanism by the renal tubules. In male rats bilateral adrenalectomy reduces protein excretion, which can be partly restored to control levels with suprarenal hormones or testosterone. Renin increases the filtration and decreases the absorption of protein only in the presence of a functioning suprarenal gland. Transient proteinuria can be produced in humans with ephedrine.

Rats with one and a half kidneys removed developed proteinuria on a standard diet. The degree of protein loss in the urine was related to the amount of protein in the diet and was independent of the development of hypertension.

[This alternative theory of the genesis of albuminuria may modify the significance attached to albuminuria in pre-eclampsia and hypertension occurring during pregnancy. Switzer *et al.* (*Amer. J. Obstet. Gynec.*, **60**, 427, 1950) have failed to demonstrate any increase in the protein content of oedema fluid in pre-eclampsia and if this is taken as evidence of normal capillary permeability to protein there seems no reason to suspect that the glomerular capillaries should differ from those of the rest of the body. Chesley (*Med. Clin. N. Amer.*, **35**, 712, 1951) in reviewing the work that has been done on renal haemodynamics in pre-eclampsia claims that constriction of the afferent glomerular arterioles is not a general finding and consequently anoxia due to vascular spasm cannot always be invoked to support the concept of a local increase in glomerular permeability as the cause of albuminuria.] *H. M. Carey*

4. **Some Hormone Studies in Normal and Toxemic Pregnancy.**

By C. W. Lloyd, E. C. Hughes, J. Lobotsky, J. Reenzo, and G. M. Avery. *J. clin. Invest.*, **31**, 1056–1063, Dec. 1952. 1 fig., 41 refs.

Serum antidiuretic activity, 24-hour urinary excretions of total corticosteroids, pregnanediol and chorionic gonadotrophin were determined in 10 non-pregnant women and in 3 subjects in the first trimester, 5 in the second, and 6 in the third trimester of normal pregnancies. In addition specimens of urine were subjected to chromatographic separation of the adrenal steroids using a benzene-formamide solvent system on paper. In this way the total corticosteroids were fractionated into "freely-water-soluble" and "poorly-water-soluble" components. The latter is related to the mineralo-corticosteroids. The results obtained in cases of normal pregnancies were compared with those obtained from 6 cases of severe and 5 cases of mild toxaemia. No significant differences were obtained in serum antidiuretic activity in non-pregnant and normal pregnant and toxaemic subjects. Excretion of total corticosteroids increased during normal pregnancy and in the last trimester many normal patients excreted amounts of corticosteroid considerably above the normal non-pregnant range. During the first trimester very little "poorly-water-soluble" corticosteroid was excreted, while during the last 3 months it constituted 25 per cent of the total corticosteroid excretion. In the severe, but not in the mild, cases of toxaemia the excretion of total and "poorly-water-soluble" corticosteroids was significantly greater than in normal pregnant women in the third trimester.

The urinary pregnanediol in toxaemic patients was lower but the chorionic gonadotrophin excretion was five times higher than in normal pregnant subjects.

H. M. Carey

5. **Hexamethonium Compounds in the Treatment of Pre-eclampsia and Essential Hypertension during Pregnancy.**

By N. Morris. *Lancet*, **1**, 322–324. Feb. 14, 1953. 7 refs.

The results of treating 10 cases of pre-eclampsia and essential hypertension with pregnancy are described.

No definite evidence was obtained that hexamethonium compounds alter the course of the disease. The side effects, effect on labour, and the effect on the foetus are briefly described. *H. H. Fouracre Barns*

6. **Intravenous Veratrum Viride in the Treatment of Toxemia of Pregnancy.**

By E. J. Alban, Jr., M. S. Dennis, and C. N. Swanson. *Amer. J. Obstet. Gynec.*, **64**, 1083–1092, Nov. 1952. 4 figs., 8 refs.

Ten cases of toxaemia, either severe pre-eclampsia or eclampsia, were treated by intravenous Veratrone. The patient is given an initial dose of 0.2 ml. of Veratrone diluted in 1 ml. of 5 per cent glucose, the drug being given slowly over a period of 3 minutes. The blood-pressure begins to fall within 5 minutes, and the fall, which is dramatic, usually lasts about 1 hour, after which time it slowly climbs to former levels. The drug is then given by intravenous infusion in 5 per cent glucose in water with the rate regulated so as to deliver an hourly amount of 0.2 ml. of Veratrone. Careful check must be made every hour on blood-pressure and pulse, and adjustments made in the rate of flow according to response. No other treatment was given except mild sedation with barbiturates. There was no evidence that the Veratrone depressed urine output but nausea and vomiting are sometimes troublesome. In some cases marked bradycardia is produced which cannot be differentiated from heart block except by electrocardiogram. In one case it was promptly relieved by atropine.

In all the cases the blood-pressure was well controlled, allowing labour to be induced by pitocin. There were no maternal deaths but there were 4 still-born infants or neonatal deaths; 3 of these were under 7 months' gestation. The intravenous infusion was maintained in 1 case for 4 days and this was aided by adding 10 units of heparin to each 1,000 ml. of fluid.

[It is well to be reminded again of the possible value of Veratrone in eclampsia. One of the most frequent causes of death in eclampsia is massive haemorrhage over the base of the brain and the danger of it is very great if the blood-pressure is over 180 mm. One of the disadvantages of Veratrone is that its effect is so temporary. What we badly want is a drug that will safely lower the blood-pressure in severe toxaemia before the foetus is viable, say at the 33rd week, and keep it down for 3 or 4 weeks.] *F. J. Browne*

7. **The Value of Vitamin E in the Treatment of Toxaemia of Late Pregnancy.**

By J. L. Mastboom and A. Sikkel. *Gynaecologia, Basle*, **134**, 391–396, Dec. 1952. 1 table, 11 refs.

Eight patients with toxaemia of late pregnancy were given in addition to a salt-free, low-protein diet, 300 mg. of vitamin E daily.

The results obtained showed that it is not possible to conclude that vitamin E has a beneficial effect on an already existing toxaemia, nor that vitamin E is of value in preventing toxaemia in pregnant women suffering from vascular or renal disease.

Josephine Barnes

8. **The Importance of Adreno-Cortical Steroids for the Development of Toxaemia of Late Pregnancy.**

By J. L. Mastboom. *Gynaecologia, Basle*, **134**, 217–243, Oct. 1952. Bibliography.

On the basis of evidence as recorded in the literature, which is reviewed at considerable length, the author postulates a theory of the pathology of pre-eclampsia based upon abnormal corticosteroid activity.

Firstly, from the literature relating to normal pregnancy, he notes the following points: (*a*) That constant hyperfunction of the anterior lobe of the pituitary is not established. (*b*) That a slight increase of corticosteroids is normally found. (c) That although there is definite evidence of increased activity of desoxycorticosteroids and 11-oxycorticosteroids, hyperfunction of the adrenal cortex is by no means proved.

Secondly, from the literature relating to pre-eclampsia he notes: (*a*) That histological studies do

not support the presence of hyperfunction of the anterior lobe of the pituitary. (*b*) That, although increased excretion of corticosteroids is established especially when oedema is present, the evidence as to the existence of hyperfunction of the adrenal cortex is inconclusive. (*c*) That pre-eclampsia is associated with decreased pregnanediol excretion, possibly due to decreased progesterone production. (*d*) There is marked similarity between the clinical picture in pre-eclampsia and desoxycorticosterone intoxication.

From these points, the author deduces the possibility of extra-adrenal production of hormones similar to the corticosteroids. This theory is lent support by reports in the literature of animal experiments and clinical observations, the foetal adrenals and the placenta both being cited as possible sources, the latter being much more probable.

On the basis of these observations, the author develops a hypothesis that pre-eclampsia [which he refers to as "toxaemia of late pregnancy"] may be due to the placental production of an excessive amount of corticosteriods. In support of this theory, he makes the following observations:

(*a*) That a likely starting-point is insufficient blood supply to the placenta. (*b*) There is marked similarity between pre-eclampsia and desoxycorticosterone intoxication. (*c*) The excretion of corticosteroids is increased in pre-eclampsia and there is evidence that the excess is extra-adrenal in origin. (*d*) Pregnanediol excretion is decreased in pre-eclampsia, probably owing to deficient progesterone production. (*e*) There is a marked structural similarity between desoxycorticosterone and progesterone, and there is evidence that the former can replace the functional activity of the latter, and further that normally in the placenta desoxycorticosterone is produced and converted, at least in part, into progesterone. (*f*) There is evidence that in pre-eclampsia the patient is abnormally sensitive to the action of vasopressin, and there is experimental evidence that such sensitization can be produced by desoxycorticosterone.

The author's theory is that, under the influence of certain predisposing factors [which are not specified], the placental blood supply becomes insufficient, with a resultant fall in the placental oxygen level. This in turn results in interference with the conversion of desoxycorticosterone into progesterone, and thus in raised desoxycorticosterone activity. The increased amount of desoxycorticosterone released from the placenta sensitizes the patient's vascular system to vasopressin, and widespread vasoconstriction occurs, producing, among other effects, both hypertension and albuminuria.

M. Halden Lloyd

9. **Inferior Placental Villi.** [In English.]

By R. Polák. *Ned. Tijdschr. Verlosk.*, No. 3, 143–159, 1952. 6 figs., 7 refs.

The author examined 118 placentas at term from the following groups:

Twenty-five normal women, 25 patients with moderate toxaemia [criteria not specified], 25 patients with severe toxaemia, 25 Rh negative patients delivered of Rh positive babies [only one woman in this group developed Rh antibodies], 18 Rh negative patients delivered of Rh negative babies.

The criteria of inferiority of placental villi were: (*a*) complete necrosis of the villus, (*b*) microinfarcts involving at least one quarter of diameter of the villus, (*c*) a villus one quarter of the surface of which was covered by fibrin or fibricoid matter. Fibrin compresses the villi and thus prevents bathing of the villi in maternal blood.

In the severe toxaemia group 55.6 per cent of the villi were inferior according to the above criteria. In all other groups combined the average incidence of inferior villi was 32.3 per cent, the lowest being 28.6 per cent in Rh negative mothers with Rh negative babies, and the highest 37.3 per cent in Rh negative mothers with Rh positive babies. Villi covered with fibrin numbered 36 per cent in placentas from patients with severe toxaemia against 22 per cent in all other groups combined. The number of inferior villi as well as the number of fibrin-coated villi in the group of patients with severe toxaemia of pregnancy was much higher than in all other patients. The corresponding figures in moderate toxaemia were normal.

The birth weight of babies born to women suffering from severe toxaemia of pregnancy is shown by the author to be lower than that of babies born of normal pregnancies. He suggests that this subnormal weight may be due to altered nutrition of the foetus because of placental inferiority. The average weight of the placentas in the various groups of patients was about the same except that with heterospecific pregnancy the placental weight was higher irrespective of sensitization.

The author suggests that the histological findings in his study support the conception that induction of labour is indicated in patients with toxaemia.

L. A. Cruttenden

10. **Retroperitoneal Hemorrhage Complicating Pregnancy.**

By B. P. Zummo, P. C. Williams, and M. Uznanski. *Surg. Gynec. Obstet.*, **95**, 512–518, Oct. 1952. 21 refs.

Retroperitoneal haemorrhage complicating pregnancy is an uncommon but by no means a rare condition. Conditions from which the retroperitoneal haemorrhage must be differentiated are ruptured spleen or peptic ulcer, biliary or renal colic, ruptured ectopic pregnancy, ruptured uterus, or ruptured varicosities, twisted ovarian cyst, or premature separation of the placenta.

The authors report 4 cases, which bring the number of published cases up to 48. Two of their patients died from rupture of an aneurysm of the splenic artery, one from rupture of an aneurysm of the left renal artery, and one from haemorrhage probably from a branch of the splenic artery.

Predisposing factors are either pathological, i.e., vasomotor disease including aneurysm, renal tuberculosis, or renal lipoma, or non-pathological, such as a blow, fall, or kick, coitus or labour. The authors feel that the most important contributory factors are

changes in haemodynamics occurring during pregnancy and labour and weakened vessels which are subject to increased circulatory volumes and increased systemic blood-pressures and are, therefore, more liable to rupture.

A review of the cases reported, together with their own cases, suggests that the period of gestation appears to be of no importance nor does gravidity play a significant part.

The commonest sites of rupture in order are aneurysm of the splenic artery or of the renal artery and a varix of the broad ligament. Other vessels causing haemorrhage include the left ovarian artery, the haemorrhoidal and coeliac arteries.

The authors deal in some detail with symptoms arising from aneurysms of the splenic, renal, and pelvic vessels. Seven out of 48 patients survived the catastrophe, 4 suffering from haemorrhage arising from vessels of the pelvis, 2 from splenic aneurysms and 1 from haemorrhage occurring in a renal lipoma.

Early diagnosis is difficult. Treatment consists in resuscitation of the patient by means of plasma and blood before laparotomy is performed. Pregnancy is terminated by Caesarean section or by hysterectomy.

Jean R. C. Burton-Brown

11. **Fatal Acute Renal Failure in Obstetrics.**

By K. O'Driscoll. *Irish. J. med. Sci.* 6th series, No. 325, 40–45. Jan. 1953. 1 table. 12 refs.

The writer has studied 20 cases of maternal death from acute renal failure. Three resulted from mismatched blood transfusion and are discarded. The remainder were stated to be of unknown cause, but in all 17 accidental haemorrhage (abruptio placentae) had occurred. Convincing arguments are advanced in favour of accidental haemorrhage of itself being the factor related to renal failure, and not the intercurrent factors of pre-eclampsia, shock, blood loss, tissue trauma, etc. It is suggested that three major manifestations of the syndrome exist, the separation of the placenta which has given the condition its name, the alteration of the clotting mechanism which has received a good deal of recent attention, and renal failure. One or other factor may predominate in any given case.

O'Driscoll does not consider that there is any obstetric cause of acute renal failure in abortion, except in those cases where accidental haemorrhage occurs before the foetus is viable. The rest of the cases he feels are due to the introduction of toxic substances as abortifacients, *Bacillus welchii* infections, and mismatched blood transfusion.

He notes that the renal failure following severe pre-eclampsia and eclampsia is usually transient, and records an interesting case where acute renal failure was attributed to eclampsia, but where further investigation showed that the patient had also suffered an accidental haemorrhage, which had been overlooked.

[Although the writer offers no explanation for the association between accidental haemorrhage and acute renal failure he has made a useful contribution in pointing out many of the fallacies in the previous arguments.] *R. T. Martin*

12. **The Surgical Treatment of Varicose Veins in Pregnancy.**

By F. W. Quattlebaum and J. E. Hodgson. *Surg. Gynec. Obstet.*, **95**, 336–340, Sept. 1952. 12 refs.

Varicosities were found in 66 of a series of 600 pregnant women and, of these, 33.3 per cent had had thrombo-phlebitis of varying degree during the present or a previous pregnancy and 2 cases developed non-fatal pulmonary embolus. The authors feel that as active treatment of varicose veins in surgical patients reduces the incidence of thrombo-embolic disease, similar treatment should be of value in obstetric patients.

Seventy-five per cent of the patients were treated satisfactorily with ace bandages and sylnasol injections. In the remainder, radical stripping of the veins was done, indications for operation being (1) incompetent varicose veins between pregnancies, (2) previous thrombo-phlebitis, and (3) incapacitating vulvar varicosities. In all, 23 patients received saphenofemoral ligation and stripping of the greater saphenous vein under pentothal anaesthesia. Heavy pressure dressings were applied for 24 hours after operation and the patients were allowed up on the evening of operation. Thereafter an ace bandage was applied from the ankle to the knee until removal of the sutures and the completion of postoperative injections. An average of 2.4 postoperative and 0.6 postpartum injections were required to clear the leg of any terminal varicosities. A unilateral operation was required in 12 patients and the remainder had a bilateral operation. In addition, 5 patients had operations on the lesser saphenous veins and 3 had complete excisions of vulvar varicosities.

After being allowed home in 24 to 48 hours, patients returned in one week for removal of sutures and post-operative injections. They were then supervised until after delivery and seen at intervals of 6 weeks, 6 months, and 1 year after delivery. Trauma to the veins during delivery was prevented by the use of ace bandages.

This series of patients has been followed up for periods of 2 months to 2½ years after operation and the results have been excellent in all cases.

Margaret C. S. Binnie

13. **Normal Delivery of a Healthy Female Infant after Successful Treatment of a Metastasising Adenocarcinoma of the Thyroid in the Mother with Radioactive Iodine (I^{131}).** (Normaler Partus eines gesunden Madchens nach erfolgreicher Behandlung einer metastasierenden Struma maligna der Mutter mittels radioaktiven Jods (I^{131}).)

By J. H. Müller and C. Brunner. *Schweiz. med. Wschr.*, **83**, 54–55, Jan. 17, 1953. 2 figs.

This is a report on a 27-year old woman in whom a papillary adenocarcinoma of the thyroid with secondaries in the cervical lymph-nodes had been removed in 1947. Despite intensive after-treatment with deep X-rays a second operation for cervical metastases had to be carried out 11 months later. Extensive mediastinal secondaries were found and radical removal proved impossible. Nothwithstanding the hopeless

prognosis the patient was married a few months later. Treatment with radioactive iodine was started and a total of 95 millicuries was given by mouth over a period of several months. Myxoedema developed as expected and was controlled by thyroid medication (Thyrakrin, 1 tablet daily). Control tests with weak radioactive iodine showed the patient to be completely athyreotic and no evidence of persisting tumour was found. The patient has been symptom-free for the past 3½ years.

Following the treatment with radioactive iodine there was a temporary oligomenorrhoea, but after thyroid medication menstruation became regular, with at first anovulatory cycles and, after 6 months, normal cycles. Two and a half years later the patient desired a pregnancy and was allowed to proceed after a thorough re-examination, having been warned about the considerable risks of congenital malformations after radiation therapy. She had a normal pregnancy and after a perfectly normal labour gave birth to a 50 cm. long female infant weighting 3400 g. The placenta weighed 660 g. The baby is very active and seems to have a normally functioning thyroid. *E. Wachtel*

14. **Spontaneous Rupture of the Uterus Resulting from Placenta Accreta.**

By W. B. J. SCHUYLER. *Amer. J. Obstet. Gynec.*, **64**, 427–430, Aug. 1952. 4 figs., 3 refs.

Placenta accreta is a rare cause of spontaneous rupture of the uterus and, according to the author, only 11 cases have been reported, including the present case of his own. This patient, a 33 year old gravida 2, had had a three weeks premature child 15 years before, the delivery being complicated by a retained placenta which had to be manually removed. Three weeks after delivery, curettage had to be done for secondary postpartum haemorrhage; since that time she had not menstruated regularly and there had been frequent episodes of menorrhagia. In April 1950 she was admitted in the 7th month of her second pregnancy. The membranes had ruptured 1 month before admission, and 1 day before admission she had complained of irregular contractions and slight bright red spotting. While in hospital she complained of occasional sharp stabbing pains in the lower left abdomen. The pain increased in intensity and 2 days after admission she vomited twice and showed evidence of acute abdominal distress, with pain all over the abdomen, sweating and thready pulse. Laparotomy showed a large quantity of free blood in the abdominal cavity and a small perforation at the fundus about 1 cm. in diameter and 3 mm. thick. Examination of the uterine wall at the site of rupture revealed a marked thinning of the wall with the placenta adherent to this portion. Attempts at removal of the placenta after incision of the uterus and removal of the foetus demonstrated the maternal surface to be greatly adherent to the uterine wall and apparently extending into the myometrium. Hysterectomy was therefore done. The patient recovered but the child died 18 hours after birth.

Examination of the uterine wall at the point of rupture revealed a marked thinning of the wall with the placenta adherent to this portion and the entire fundus. Microscopic sections showed invasion of the uterine muscle by the chorionic villi as well as considerable trophoblastic extension into the myometrium.

F. J. Browne

15. **A Hitherto Undescribed Symptom of Rupture of the Gravid Tube.** (Un sintoma, no descrito, de rotura de la trompa gravida.)

By L. TOUS SANTAMARIA. *Rev. espan. Obstet. Ginec.*, **11**, 372–375, Nov.-Dec. 1952.

The author describes a case of tubal pregnancy of approximately 10 to 12 weeks' duration with a history of severe abdominal pain following one month's amenorrhoea. Although the pain had occurred for the first time about a month after the missed period, the patient did not present herself until the pregnancy had advanced to the duration already mentioned.

The diagnosis was at first in doubt but when she was seen again 8 days after the first examination it was obvious that the case was one of ruptured tubal pregnancy. She was moved to hospital by car, the sick woman being seated with her thighs elevated and flexed, as she felt less ill in this position. "Under these conditions, although the speed of the car was not great, there was inevitably a certain amount of movement, during which the patient felt quite definitely a movement of fluid inside her abdomen and to the lower part of it. This she later compared to the sensation which is sometimes felt in the summer after having eaten gaspacho (a spicy dish of Andalusia) and having drunk a lot of water on top of it. Needless to say on this occasion the patient was fasting preparatory to the possibility of surgical intervention. This new symptom of the existence of liquid in the peritoneal cavity arose no doubt from a mass of uncoagulated blood."

The diagnosis was confirmed at operation when 500–750 ml. of uncoagulated blood, a foetus 7 cm. long and a ruptured left Fallopian tube were discovered. *D. G. Wilson Clyne*

16. **Bilateral Ovarian Dermoid Cysts with Pregnancy. Double Oöphorectomy.** (Quiste dermoide ováricó bilateral y embrazo. Ovariectomia doble parto a término.)

By PÉREZ FOLGADO. *Toko-Ginec. Práct.*, **11**, 559–562, Dec. 1952.

At a meeting of the Spanish Gynaecological Society held on the 5th March, 1952, an interesting case was reported.

The patient was a primigravida aged 29 years. On antenatal examination at 3½ months' gestation, a mass was felt abdominally to the left side of the fundus of the uterus.

On vaginal examination, another mass was felt below the pregnant uterus. On abdominal exploration, both masses were found to be dermoid cysts, arising from each ovary. Both cysts with incorporated ovary in each were removed. Postoperative treatment consisted of progesterone 5 mg. and vitamin E 30 mg. for 12 days.

The patient was delivered at term, and breast fed the baby.

Subsequently she showed signs of hormonal disturbance as the result of the bilateral oöphorectomy.

John F. Foulkes

17. **Lipoid Folliculoma of Right Ovary Associated with Normal Pregnancy at 8th Month.** (Folliculoma lipidoco dell'ovaio destro concomitante a gravidanza normale all'ottavo mese.)

By P. Bailo. *Riv. Ostet. Ginec., Pract.*, **25**, 580–587, Dec. 1952. 5 figs., 23 refs.

The author describes a case of granulosa cell tumour of the ovary associated with viable pregnancy in a woman aged 36. Menstruation began at 15 years, recurred at regular intervals until the first pregnancy in 1947, which resulted in spontaneous delivery of a live boy. Normal menses returned in due course. The patient was first seen in 1950 during the 35th week of her second pregnancy. Previously well, she complained of breathlessness and recent increase in weight. Examination did not reveal any abnormality. Abdominal enlargement was consistent with pregnancy at term. A single foetus, presenting by the vertex, was outlined easily.

Hydramnios was the diagnosis. Labour was induced surgically. The patient was delivered of a live girl, weighing 4 pounds 15 ounces (2,250 g.). Following expulsion of the placenta examination disclosed a firm, globular, mobile tumour, the size of a man's head, on the right side behind the uterus.

Laparotomy was performed on the 7th day postpartum. The abdomen contained 3½ pints (2 litres) of pinkish fluid. The serosal surfaces were free of any tumour implant. The right ovary was replaced by a solid tumour; this was removed. The uterus was involuting normally. The left ovary was normal and did not contain a corpus luteum.

The tumour was ovoid, weighed 4 pounds 15 ounces (2,250 g.) and measured 8 × 7 × 5 inches (21 × 18 × 12 cm.). The external surface was smooth and grey-yellow. The cut surface was lardaceous, yellow-white, and showed a few cystic areas. Histological examination revealed a granulosa-cell tumour with follicles and scattered lutein-like changes.

The patient's convalescence was complicated by transient pleurisy. She was discharged with the baby on 18th postoperative day. The author considers this patient's case to be the eleventh reported. He believes that the tumour did not have any deleterious influence on the pregnancy; rather, he supposes the pregnancy to have stimulated the tumour to rapid growth.

[Precipitate reports on ovarian tumours, without proper follow-up, neglect the vital question of malignancy. This one shows the need for the support of a tumour registry.] *M. Caturani*

18. **Parotitis During Pregnancy.**

By O. Ylinen and P. A. Järvinen. *Acta obstet. gynec. scand.*, **32**, 121–132, 1953. 2 figs., 26 refs.

Working at the First and the Second Women's Clinic of Helsinki University, the authors have collected 13 cases of maternal parotitis (mumps) which were observed in that city during the period 1949–50. In 7 of these cases infection occurred during the first 3 months of pregnancy, that is during the "critical period for the appearance of congenital malformations" as described by Gregg and by Swan for rubella. Three of these pregnancies ended in miscarriage 3 to 14 days after the onset of mumps, 2 resulted in the birth of apparently normal babies at term, and in the remaining 2 cases an abnormal infant was borne; one of them was a premature stillbirth with the right leg, the right side of the pelvis, the anus and the external genital organs missing (permission for necropsy was not given); the other died following entero-anastomosis performed for extensive atresia of the ileum.

In 6 instances parotitis occurred during the second and third trimester of gestation. In one of these cases a mongoloid infant was born, subsequent to infection with parotitis in the fourth month of pregnancy, but this mother had a toxoplasmosis infection coinciding with the parotitis. In one case parotitis occurred in the seventh month of pregnancy and was followed by premature delivery 9 days after the onset of the disease. The remaining 4 pregnancies were uneventful and the children were apparently normal.

The author's conclusion that parotitis occurring during the first trimester of pregnancy can damage the foetus and be responsible for congenital malformations is further substantiated by 98 similar cases in the literature.

[There are no controls to this small series. The country-wide survey of the influence of maternal virus diseases on pregnancy, now under review by the Ministry of Health in London, should shed light on this problem.] *N. Alders*

19. **Pregnancy Complicated by Miliary Tuberculosis.** (Ciaza powiklana gruzlica prosowkowa.)

By E. Kowalski. *Ginek. Polska*, **23**, 329–334, July-Oct. 1952.

The author describes a case of spontaneous abortion due to miliary tuberculosis of pulmonary origin treated with streptomycin.

Both foetus and placenta were examined histologically for tuberculous lesions. The results were negative, and were subsequently confirmed by guinea-pig inoculation with the emulsion of foetal organs, placenta and liquor amnii: these results were again confirmed by trial cultures on Petraniani media, and finally by tissue smears for tubercle bacilli by the Ziehl-Neelsen method. Seven weeks later the patient was walking and gaining weight; clinical and radiological lesions in the lungs receded markedly. Repeated pelvic examinations in the course of 9 months did not reveal any pathological lesions of the patient's reproductive organs.

The author reviews the literature of pregnancy complicated by miliary tuberculosis. He also points out the danger of miliary dissemination, which may take place in consequence of any manipulations of the reproductive organs infected with tuberculosis. The cause of the spontaneous abortion in this case was the poor general condition of the patient. The restriction of breathing and the increased oxygen need of the systemic tissues, and also of the placental circulation, caused severe dyspnoea, and finally fibrosis of the placenta led to the death of the foetus.

S. H. Riterband

20. **Immunity of the Newborn. A Study of the Transfer of Anti-streptolysin from Mother to Foetus during Pregnancy.**

By J. MURRAY and R. M. CALMAN. *Brit. med. J.*, **1**, 13–15, Jan. 3, 1953. 9 refs.

Interest in the transfer of antibodies across the placenta has increased since the observation that cord blood may contain more antibody than that of the mother. Recent work has mainly concerned diphtherial and staphylococcal antibodies.

In the present investigation, the anti-streptolysin O titre of the maternal and cord blood at the time of delivery was estimated in 46 cases. It was found that the cord blood contained more anti-streptolysin than the maternal blood in 41 cases, the levels were approximately equal in 3, the maternal level was higher in 1 and, in 1 case, the levels were too low for the test.

The significance of these findings and the revised view of placental permeability to antibodies to which they lead has been discussed elsewhere (Calman and Murray, 1951, *Endeavour*, **10**, 27). The authors then concluded that the simple filtration theory was becoming untenable and their present results support that opinion. *Doreen Daley*

21. **Ectopic Pregnancy. A Clinical Study of 136 Consecutive Cases.**

By H. D. PRIDDLE, C. W. MOULTON, and M. S. DENNIS. *Amer. J. Obstet. Gynec.*, **64**, 1093–1101, Nov. 1952. 14 refs.

This series of cases was treated in the 2½ years beginning January 1st, 1949. In 8 there had been a previous tubal pregnancy; in 23 the pregnancy was the first and of those who had had a previous pregnancy, the interval since last pregnancy was more than 4 years in 54 per cent. The incidence of previous salpingitis revealed by examination of the excised tube was 28 per cent. There was a history of amenorrhoea in 81 per cent, abdominal pain was present in 90 per cent, irregular vaginal bleeding in 61 per cent, shoulder pain in 0.7 per cent, syncope in 31 per cent, nausea and vomiting in 9 per cent and rectal pain in 2 per cent. Shock and a blood-pressure of less than 90 mm. of mercury systolic was noted in 33 per cent; 3 of these were found at laparotomy to have an unruptured tubal pregnancy and only a small amount of blood-tinged peritoneal fluid was present in the abdomen. The chief finding on internal examination was tenderness on manipulation of the cervix which the authors consider to be the important diagnostic finding on pelvic examination. They also find needle aspiration of the cul-de-sac to be very helpful. It was done through the vaginal vault in 129 of the 136 cases. In 123 the fluid was "grossly bloody", the other 6 patients yielding only a very small amount of clear or cloudy peritoneal fluid.

The pregnancy was interstitial in 2 cases, secondary abdominal in 4 and tubo-ovarian in 1. Pathological study noted a ruptured tubal pregnancy in 124 cases (91 per cent), an unruptured tubal pregnancy in 5 cases and tubal abortion in 7. All but 20 patients received blood transfusions before, during, and after surgery. Evacuation of the affected tube and salpingostomy was done in 4 women who had had a previous tubal pregnancy and salpingectomy. Additional elective surgery is very rarely warranted and appendicectomy should never be done. The mortality was 2.9 per cent (4 deaths) but only 2 were due to the ectopic pregnancy.

[This is a useful paper. The authors rightly emphasize the value in diagnosis of tenderness on manipulation of the cervix and of aspiration of the pouch of Douglas and the danger of removing the appendix at ectopic pregnancy operations. Might it not have been possible to save some more of these tubes especially in childless women and in whom the opposite tube is quite often occluded? It would be useful if operators would routinely record the state of the other tube in all cases.] *F. J. Browne*

22. **A Study of 245 Cases of Ruptured Ectopic Pregnancy.**

By W. O. JOHNSON. *Amer. J. Obstet. Gynec.*, **64**, 1102–1110, Nov. 1952. 4 figs.

In this series, collected in one hospital in the 24 years preceding 1951, chronic salpingitis was reported in 51 per cent of the 245 cases; 17 of the ectopic pregnancies were first pregnancies; 5 patients were married twice with ectopic pregnancies in both marriages; there were 2 cases with ectopic pregnancy in one horn and a normal pregnancy in the uterus, and there was one patient with a ruptured ectopic pregnancy in one tube and an unruptured pregnancy in the opposite tube. The average time between the previous and the ectopic pregnancy was 5.2 years, and the interval varied from 10 to 18 years. The author thinks that the Aschheim-Zondek test is of little value in diagnosis, and considers that "posterior colpotomy", with aspiration of cul-de-sac bloody fluid, is one of the simplest diagnostic aids, and is reliable in 96 per cent of the cases. It is relatively simple and "fairly safe", and should be done in every case where ectopic pregnancy is suspected. Thirty-eight per cent of the patients had appendicectomies at the operation but the author believes that removal of the appendix in "acute manifest cases" (cases with signs of internal haemorrhage) is meddlesome surgery; 21 per cent of the 89 obscure cases (in which the products of conception and haemorrhage are walled off) had hysterectomy, all of which in the author's opinion "were justified". The mortality rate for the whole series was 2.4 per cent.

[It is not clear what the author means by "posterior colpotomy with aspiration of cul-de-sac bloody fluid". This seems to be a more elaborate procedure than simple aspiration by needle, and why does he say it is "fairly safe"? Is there not some risk of aspirating the bowel? I have never liked the method and perhaps have been prejudiced against it by getting only clear fluid in a case (the only one in which I used it) that laparotomy revealed to be a ruptured tubal pregnancy. Besides only 96 per cent reliability does not much recommend it.] *F. J. Browne*

23. **Ectopic Pregnancy with Implantation into the Liver.** [In Russian.]

By A. G. SEREBRIAKOVA and N. N. KANSHIN. *Akush. Ginek.*, No. 5, 90, 1952.

The case of a rare implantation of the ectopic pregnancy is presented. The patient, a young woman of 29, was operated on because of a tumour of the right epigastrium, associated with 2½ months of amenorrhoea and attacks of sharp pain in the same area.

In the course of explorative laparotomy a 3-months old foetus was found. The placenta together with foetal sack was removed from the Glisson capsule of the right lobe of the liver. The total mass was of the size of an adult human head. Slight operative haemorrhage was controlled by stitching the liver in layers, followed by transfusion of 400 ml. of blood. The postoperative course was uneventful. *E. W. Collis*

LABOUR

24. **The Emergency Obstetrical Service. A Review of 489 Cases in the Manchester Area.**

By G. J. DEWHURST. *Lancet*, **2**, 746–751, Oct. 18, 1952. 8 refs.

The author was connected with the Emergency Maternity Service in the Manchester Region between September, 1947, and December, 1950, during which time 489 patients were treated—mainly for complications of the third stage of labour. The team consisted of a registrar and a sister. Group O Rh−ve blood was used.

There were 245 cases of retained placenta. Shock was present in 63 per cent. The practitioner was asked in the meantime to give 0.5 mg. of ergometrine intramuscularly and to control the fundus. On the team's arrival blood transfusion was begun if necessary. If the placenta had already separated and was lying in the lower uterine segment or vagina it was delivered by cord traction, as being less disturbing to the patient. Otherwise expression might be attempted in the absence of shock. Usually, however, manual removal was performed as soon as the patient's condition began to improve. It was performed in 71.4 per cent of cases. Blood transfusion was given in 73 per cent. The author deplores the fact that 17 of these patients had already been delivered by forceps under inhalation anaesthesia, and feels that the practitioner should have been prepared to proceed to manual removal of the placenta himself. There were 2 maternal deaths in this group.

One hundred and forty-three patients suffered from postpartum haemorrhage and collapse following the third stage. There were 5 maternal deaths in this group. Shock was present in 72 per cent. Transfusion was given in 74.8 per cent. Twenty-eight patients had been given crude pituitary extract, and these were among the most severely shocked. The author condemns its use entirely for the third stage. He emphasizes the importance of keeping the uterus empty by fundal control, blood in the uterus greatly increasing shock, as well as preventing good retraction.

He stresses also the danger of postpartum haemorrhage in the multigravida with many previous pregnancies, especially in the presence of chronic anaemia, and feels she should be delivered in hospital. A history of previous third stage complications should also be an indication for hospital delivery.

Eileen D. M. Wilson

25. **An Obstetrical Analysis of the Action Potentials of the Uterus in Labour (Electro-uterography).** (Analyse obstétricale des potentiels d'action de l'utérus en travail (electro-uterographie).)

By E. LÉVY-SOLAL, P. MORIN, and F. ZACOUTO. *Presse méd.*, **60**, 1335–1338, Oct. 8, 1952. 8 figs., 15 refs.

The electric potentials associated with uterine action were investigated by studying (*a*) fresh uterine muscle strips immersed in isotonic solution at body temperature, (*b*) exteriorized uterine muscle at Caesarean section, and (*c*) intact uterine wall by means of needles through the abdominal parietes. In further trials electrodes were placed on the cervix and abdominal wall and, finally, two abdominal electrodes were used. All methods gave comparable results but the last was used on account of its technical simplicity and lack of discomfort to the patient.

The results of study of the tracings from over 100 women in labour showed that, by this method, uterine action could be divided into 3 types—normal physiological, inert, and hypertonic. It appeared that differences of tone demonstrated by this means could not always be appreciated by palpation or simple mechanical recording of contractions and the authors point out that rational therapy in dystocia can only be instituted if the uterine tone is known. They advise anti-spasmodics in hypertonic inco-ordinate action and pitocin (5 units in 500 ml. glucose saline given intravenously at the rate of 20-30 drops per minute) when the tone is low.

In discussing the use of artificial rupture of the membranes, they warn against it as routine practice to accelerate labour for, though it may well increase contractions that are of normal type, it may result in complete abolition of contractions in those cases with hypotonia. *Doreen Daley*

26. **Does the Follicle Hormone Influence the Onset of Labour?** (Hat das Follikelhormon eine Bedeutung für den Geburtsbeginn?)

By Dr. M. NIEDERHOFER and Dr. A. PUCK. *Med. Klin.*, **48**, 71–75, Jan. 16, 1953. 47 refs.

Quantitative estimations of follicle hormone from the urine of 24 pregnant women before term and during labour were carried out by means of the Allen Doisy test. No relationship between the level of follicle hormone excretion in the urine and the onset or course of labour was apparent. The authors then investigated the interrelationship between oestrogen and progesterone metabolism. They state that in the 38th week of pregnancy, the time of maximum excretion of all oestrogenic substances and pregnanediol, the percentage of oestradiol among the urinary oestrogens is lowest. They conclude therefrom that the rise of oestradiol excretion is caused by an increase in formation and that this process, owing to a simultaneous rise in progesterone production, is accompanied by an

accelerated conversion of oestradiol into oestrone and oestriol.

After the 38th week there is a slow decrease in oestrogen and pregnanediol excretion, but the oestradiol percentage rises, which may mean that slow formation is accompanied by even slower conversion. Oestradiol excretion is markedly raised at the onset of labour and decreases during the course of labour.

This means a remarkable change in oestrogen metabolism which seems even more pronounced at the onset of labour and may be significant for it. These experimental results prove the absence of an antagonistic action between the follicle hormone and progesterone.

There is no change in the excretion of gonadotrophic hormone and androgenic substances towards the end of pregnancy and during labour. *E. Wachtel*

27. **A New Method of Administration of Oxytocin during Labour: Slow Continuous Perfusion by the Deep Subcutaneous Route together with Hyaluronidase.** (Une nouvelle méthode d'administration des extraits ocytociques post-hypophysaires au cours de l'accouchement: la perfusion lente continue par voie sous-cutanée profonde associée à l'hyaluronidase.)

By L. Digonnet, J. Cahn, and J. Roy. *Presse méd.*, **60**, 1191–1192, Sept. 13, 1952. 33 refs.

The authors have encountered difficulties in their method of administering oxytocic substances by the intravenous route to the parturient patient, and have evolved a more satisfactory technique by deep hypodermic injection. Five hundred ml. of normal saline are given by subcutaneous drip into the anterolateral aspect of the thigh and, when a swelling the size of a tangerine is produced, 250 Schwenk units of testicular hyaluronidase are injected into the delivery tube. When a rate of 10–20 drops per minute is attained, 5 units of posterior pituitary extract (free from vasopressor factor) are added. The result in 14 patients suffering from prolongation of labour due to inertia was to increase uterine action to a normal physiological level with subsequent normal or forceps delivery. Two cases were failures due to obesity, and in these the authors recommend doubling or tripling the dose of hyaluronidase.

The need for strict asepsis is emphasized as hyaluronidase will also disseminate widely any contaminating organisms which may be present.

C. W. F. Burnett

28. **Inefficient Uterine Action.**

By T. N. A. Jeffcoate, K. Baker, and R. H. Martin. *Surg. Gynec. Obstet.*, **95**, 257–273, Sept. 1952. 6 figs., 16 refs.

Inefficient uterine action is classified into the following 4 groups, more than one of which may occur simultaneously.

1. Hypotonic inertia. This is true inertia and labour may continue for days without much risk to mother or child. It may occur at any time during labour.

2. Hypertonic states. (*a*) Hypertonic lower segment and internal os. This may be confused with hypotonic inertia but is distinguished by the presence of severe low backache. Occasionally, when resistance occurs at the internal os and the presenting part remains high, it may be regarded as constriction ring dystocia. (*b*) Colicky uterus. (*c*) Constriction ring dystocia. This is a continuation of hypertonic lower segment or colicky uterus and must be distinguished from a retraction ring. All hypertonic states are characterized by a persistently raised intra-uterine pressure which interferes with placental circulation and jeopardizes the foetus, even when the membranes are unruptured. There is discomfort between contractions, prolonged labour with unusually distressing pains and the cervix dilates slowly and remains thick and oedematous. Sometimes during a long first stage the patient bears down. This is apparently due to a spasm in the rectum and pelvic colon from a disturbed sympathetic nervous system. This may also cause the distension of stomach, descending colon, and bladder which commonly occur.

3. Asymmetrical uterine action is only an important cause of dysfunction where there is incomplete fusion as in uterus bicornis unicollis or uterus subseptus.

4. Cervical dystocia. Primary cervical dystocia only occurs in primigravidae and usually causes inertia. It may occur in multigravidae after injury or disease of the cervix and cause rupture of the uterus. Spontaneous annular detachment results occasionally from prolonged arrest of circulation together with the retracting uterus pulling against the resistant external os.

The authors review a series of 277 cases from Mill Road Maternity Hospital, Liverpool Maternity Hospital, and private practice. All minor degrees of inertia are excluded and the overall incidence is between 0.8 per cent and 1.5 per cent. One hundred and thirty-nine patients were delivered vaginally and the remainder by Caesarean section during the first stage, after average duration of labour of 55 hours and 52 hours respectively. Ninety-five per cent of cases occur in primigravidae, the remainder being due to colicky uterus or true inertia in multigravidae or where previous delivery has been by Caesarean section. There is only a slight increase in incidence in elderly primigravidae. The time of rupture of the membranes and overdistension of the uterus do not affect the incidence.

Uterine inertia is no more common with breech than with vertex presentations but is associated with occipito-posterior positions or transverse arrest of the head. Cephalo-pelvic disproportion is also a common cause. A high presenting part without disproportion may be due to hypertonicity of the lower segment before labour preventing engagement of the head. False labour represents inefficient uterine action also.

A careful vaginal examination to exclude disproportion and malposition should be done and X-ray examination if possible. The type of disorder should be determined then and if there is doubt as to whether the patient is really in labour adequate sedation should be given. If uterine action ceases the patient is not in labour.

Intravenous drip infusion of 5 per cent glucose solution should be given if acetonuria appears. This improves uterine action in addition to its general effect. Artificial rupture of membranes may be effective in true inertia only. Posterior pituitary extract can be

used in selected cases of true inertia and the authors give 5 units of oxytocin in 1,000 ml. of 5 per cent glucose solution intravenously. This can be controlled rapidly by adjusting the stopcock. Too large a dose may affect the foetus by raising the uterine tone and, if given too long, the uterus may become refractory and not respond to further treatment.

Other treatment consists in allaying pain and anxiety and reducing muscle spasm. Morphia with or without hyoscine or barbiturates is valuable but pethedine is safer and can be given in the intravenous drip in a solution of 300 mg. to 1,000 ml. of glucose saline. Speed of administration is varied by controlling the drip and 600 to 800 mg. can be given in 24 hours.

The authors have not found sympathetic depressants to be of value and have no experience of treatment by interruption of the autonomic nerve pathways. Oestrogens do not affect the uterus in labour.

Forceps delivery should be done if there is no disproportion and the cervix is fully dilated. Incision of cervix and forceps delivery during the first stage may be done in cervical dystocia only. The vertex must be presenting and engaged and the cervix completely effaced, thin, and at least half dilated. Lower segment Caesarean section is the best method of operative delivery in all other cases, usually under general anaesthesia.

The maternal and foetal mortality are now about 1 per cent and 15 per cent respectively. In this series there were no maternal deaths and the foetal mortality was 12 per cent for 101 cases reported in 1949 and 3 per cent for 176 cases since.

Of 147 cases delivered by forceps or Caesarean section between 3 and 13 years ago, about 50 per cent have not conceived again and the infertility was voluntary in one third of these. In the remainder, uterine action became increasingly efficient during subsequent labours. Fear would not, therefore, seem to be a cause of inefficient uterine action.

Margaret C. S. Binnie

29. **Evaluation of Intravenous Pituitrin.**

By S. LUBIN, R. WALTMAN, L. TISDALL, and S. R. M. REYNOLDS. *Amer. J. Obstet. Gynec.*, **64**, 248–259, Aug. 1952. 3 figs., 14 refs.

Since 1948 the authors have used pituitrin by intravenous drip in over 1,000 cases. They personally use 1½ to 2 minims of pitocin or pituitrin in 500 ml. of 5 per cent glucose well dissolved in distilled water or normal saline in a dispensing bottle delivering 30 drops per minute or 120 ml. (¼ minim) per hour. If, as rarely occurs, the uterine response is not good the rate of administration is increased normally to 60 drops a minute, or 1 minim per hour in 250 ml. of diluent. Demerol or other adequate sedation must be used as necessary. The drip can be used for induction of labour but, if the membranes are intact, the results are not good. The authors therefore rupture the membranes artificialy in such cases. With the intravenous drip it is essential that the obstetrician be present at the patient's bedside at all times to observe the effect on the uterine contractions and any changes in the foetal heart rate. If the dosage is ¼ minim per hour there is very little chance that abnormal uterine contractions of sufficient intensity to rupture a uterus will result, but changes in the foetal heart rate may be observed very quickly if higher concentrations of pituitrin are used. It is essential that the cervix must be prepared or " ripe " for labour when the intravenous drip is begun. If the labour does not seem to be progressing as evidenced by increase in the intensity and duration of the contractions along with the continuous steady dilatation of the cervix, pituitrin is indicated. If there is delay attributable to decreased efficiency of uterine contractions, intravenous pituitary drip results in increased incidence of spontaneous rotation of the foetus from the posterior and transverse position. This method has reduced to a minimum the number of manual or instrumental rotations and mid-forceps deliveries without any increase in foetal or neo-natal deaths. Among contra-indications to its use are contracted pelvis, large breech, high parity with large foetus, twins with overdistension of the uterus and intact membranes, abnormal presentation, and previous section or hysterotomy.

Though contracted pelvis is regarded as a contra-indication the authors regard the drip as safe and useful in many cases of borderline cephalo-pelvic disproportion without pelvic contraction. In such cases the labour is often desultory. By rupturing the membranes artificially if they are intact and the use of the drip for a few hours at most, an early decision as to the best method of delivery may be made. With the onset of adequate contractions and if there is no progress made within one to two hours an immediate Caesarean section is indicated. With this regime many cases which in the past would have had abdominal delivery are now successfully delivered by the vaginal route.

F. J. Browne

ANAESTHESIA

30. **The Relief of Pain in Childbirth.**

By F. N. REYNOLDS. *J. Irish Med. Ass.*, **31**, 357–360, Dec. 1952.

The author begins by surveying the progress which has been made since chloroform was first used for the relief of pain in childbirth over 100 years ago. Progress in the relief of pain by anaesthetics and analgesics has been slow and halting and in the author's opinion this applies especially to obstetrics. The first real improvement came with the introduction of nitrous oxide and air, as given in the Minnitt machine. In the early 1940's pethidine, caudal anaesthesia and trilene were introduced and there seemed hope of real progress. The author states his belief that we now have a choice of fairly satisfactory methods of relieving pain in both stages of labour, no matter what the circumstances of the patient.

Early in the first stage of labour chloral hydrate and bromide (30 gr. of each) is advised but it is explained that these drugs are of little use once labour is fully established. For the patient suffering from cardiac disease and those in whom a long and dreary first stage

is expected morphine and scopolamine are recommended. The author does not believe in repeating the dose of scopolamine in the form of so-called "twilight sleep", which was so popular a number of years ago. He feels that the risk to the baby from scopolamine as well as morphine is too great.

The author is of the opinion that caudal anaesthesia can never attain wide use in view of the technique required and the uncertainty of its effects. In the treatment of selected cases, such as cardiac disease and trial labour, it can give most gratifying results.

Pethidine is praised as one of the most useful analgesic drugs for use in the first stage of labour, but it should not be used until labour is properly established otherwise it tends to bring matters to a halt for several hours.

For the second stage of labour either gas and air or trilene is advised. The great advantages of trilene are its portability and cheapness. For the delivery of the head the author advises chloroform and in his opinion the danger of chloroform poisoning is minimal.

So far as private patients are concerned the author feels that the present position in regard to relief of pain is satisfactory but for the bulk of patients attended by midwives the situation is unsatisfactory. The midwife is brought up to believe that the relief of pain in labour is unnecessary and methods which are available to midwives are by no means used as freely as they should be. The author does not believe that the best midwifery is done by midwives and stresses their lack of equipment, facilities and knowledge.

For use by the midwife he recommends pethidine in the first stage of labour and trilene in the second stage.

In conclusion the author suggests that every region should have appointed to it an obstetrician interested in the problem of analgesia and anaesthesia and whose particular duty it should be to teach, advise, and help the midwives and the patients under their care.

[A number of people might take exception to some of the author's observations in regard to midwives but there is undoubtedly need for a more realistic approach to the relief of pain in labour in domiciliary midwifery. The author's suggestion that caudal anaesthesia is suitable for cases of trial labour is surprising. Hingson and subsequent workers have all emphasized the danger of using caudal anaesthesia in the presence of disproportion. Painless dilatation of the lower segment followed by rupture of the uterus may occur if this warning is unheeded.] *J. K. Russell*

31. **Pure Nitrous Oxide in Labour.**

By A. KINCH. *Acta obstet. gynec. scand.*, **32**, Suppl. 2, 1953.

This monograph of 79 pages deals with the results of experimental and clinical investigations of the blood-gases in relation to intermittent administration of pure nitrous oxide (N_2O) for the purpose of relieving pain during labour. These investigations were carried out at the pharmacological department of the Karolinska Institutet and at the Maternity Clinic Södra Barnbördshuset, in Stockholm. The author's material consisted of 196 healthy women selected at random and of 61 controls; pure N_2O, alternating with air, was given through a face mask from an "analgesia machine" to the test subjects, while the controls did not receive any medication.

These are some of the results. With a single inhalation of N_2O, the CO_2 concentration of venous blood showed a gradual decline from the commencement of the inhalation until its end, while in arterial blood the depression persisted for 15 to 20 seconds after termination of inhalation; the longer the total duration of the N_2O administration the lower became the CO_2 concentration in venous blood. The initial values became progressively lower, but in arterial blood no similar change could be observed even when administration had continued for 2 hours. There was no reduction of the O_2 contents of venous blood with the inhalation of from 3 to 5 litres of pure N_2O, but there was brief arterial hypoxia which disappeared within 15 to 20 seconds after termination of inhalation, that is in good time before the next inhalation (60 to 80 seconds later). During and for 15 seconds after inhalation of pure N_2O, the content of this gas increased in venous blood, but in arterial blood the concentration reached its maximum at the time of termination of inhalation, and then declined rapidly.

The slight hypoxia is of no clinical significance provided that the amount of N_2O administered does not exceed 5 litres, and that there is a certain minimal interval between the inhalations, namely 60 seconds for 3 litres, 80 seconds for 4 litres, and 100 seconds for 5 litres.

Administration of pure N_2O to the mother does not harm a healthy infant if these rules are observed, for it was shown that there was no hypoxia in the blood of the umbilical vein immediately after the mother had inhaled the gas.

If pure oxygen was given to the mother during the last 15 to 35 minutes of labour, there was a marked increase of the O_2 contents of the cord blood, while O_2, if given to the mother after birth of the child but before the cord was cut, was not transferred from mother to child. *N. Alders*

PUERPERIUM

32. **An Outbreak of Streptococcal Infection in a Maternity Hospital.**

By J. GIBSON and R. M. CALMAN. *Lancet*, **1**, 320–322, Feb. 14, 1953. 4 refs.

An outbreak of 25 cases of infection due to group A beta-haemolytic streptococci between the months of November, 1952, and January, 1953, is described.

The infection occurred in the genital tract of the lying-in mothers in varying degrees of severity and responded to penicillin treatment. Other sites of the infection were the skin and throat. In spite of disinfection and isolation, the outbreak continued and was continuing at the time the article was written. It was suggested the epidemic was the result of an increase in the pathogenicity of the organism, the majority of which were insensitive to sulphadiazine.

H. H. Fouracre Barns

INFANT

33. **Prenatal Sex Determination by Vaginal Smears.** (Zur Frage der pränatalen Geschlechtsbestimung aus dem Scheidenabstrich.)

By J. ARTNER and A. KOLLER. *Schweiz. med. Wschr.*, **83**, 55–57, Jan. 17, 1953. 1 fig., 2 tables, 26 refs.

In the course of their routine cytological investigations of normal pregnancies the authors decided to check the claims of Nieburgs *et al.* (*Amer. J. Obstet. Gynec.*, **57**, 356, 1949) that specific smear patterns in pregnant women allow an accurate prediction of the sex of the foetus. These authors had described 3 specific smear pattern, i.e., the oestrogenic smear alleged to indicate a female baby, the mucoid cornified smear and the glycolytic smear found when there is a male baby.

Artner and Koller investigated 725 pregnant women of whom smears were taken at 4-weekly intervals throughout their pregnancies. Four hundred and fifty-three of these have been delivered at the time of this report. They found 4 different smear patterns: (1) the "navicular" type which occurred in 63.4 per cent of their cases, (2) the "pre-cornified" type in 13.1 per cent, (3) the "cornified" type in 2.9 per cent, and (4) the "cytolytic" type in 15.6 per cent of women. These patterns were correlated to the degree of oestrogenization and bore no relationship to the sex of the foetus. Smear appearances may change during the course of pregnancy and variations from the low oestrogen cytolytic type to the high oestrogen cornified type or vice versa have occurred in the same woman.

It is argued that an influence of sex specific foetal hormones on the maternal vaginal epithelia could only be assumed if it were proved that the foetus produced hormones and that these hormones were present in sufficient concentration to exert an appreciable effect on the maternal hormonal level. *E. Wachtel*

34. **Breast-feeding in the Oxford Child Health Survey. Part 1: A Study of Maternal Factors.**

By C. WESTROPP. *Brit. med. J.*, 138–140, Jan. 17, 1953. 26 refs.

This investigation relates to 574 mothers who regularly attended the Oxford Child Health Survey for at least a year. Its purpose is to compare the circumstances of mothers who failed to establish or maintain lactation with those who succeeded.

The mean duration of complete breast feeding was 5.3 months, and of partial breast feeding 3.7 months; 53.8 per cent breast-fed completely for over 4 months; 30 per cent maintained complete breast feeding for more than 3 weeks but less than 4 months. In 16.2 per cent lactation was never firmly established.

The effect of age and parity was investigated. There were 264 primiparae; 111 were under 25 years—11 per cent failed completely and 42 per cent continued over 4 months. One hundred and thirteen were between 25 and 34 years. Nine per cent failed completely and 65 per cent continued over 4 months. Twenty were over 34 years—25 per cent failed and only 35 per cent continued over 4 months. For multiparae there was no distinction by age.

When both parity and social class were considered, two distinct trends appeared. For mothers in social classes I and II the incidence of prolonged breast feeding increased steadily with increasing size of family. In all other classes, mothers with 2 or 3 children were more successful than either primiparae or mothers with four or more children. Previous experience of maternity had a favourable effect on lactation, but not enough to offset the adverse effects of overwork and poverty.

Successful lactation bore no relationship to physique but was more common in those in good health.

In studying economic circumstances an "amenities rating" was applied, taking into consideration housing, overcrowding, etc. Twenty per cent were favourably rated, 56 per cent moderately, and 24 per cent severely handicapped. The corresponding figures for prolonged breast feeding were 64 per cent, 54 per cent, and 43 per cent. Similar figures resulted from an attempt to assess maternal efficiency.

Less than half the survey babies were born at home—the overall incidence of prolonged breast feeding in these was 50 per cent. Mothers in social classes I and II and delivered in institutions showed the highest percentage of prolonged breast feeding in the survey—68 per cent. The author feels this emphasizes the importance of freedom from domestic worries during the early days of lactation. *E. Wilson*

35. **Experimental Erythroblastosis Fetalis in Rabbits. 1. Characterisation of a Pair of Allelic Blood Group Factors and their Specific Immune Isoantibodies. 2. The Passage of Blood Group Antigens and their Specific Antigens across the Placenta.**

By A. KELLNER and E. F. HEDAL. *J. exp. Med.*, **97**, 33–49, 51–60, Jan. 1953. 49 refs.

These workers at the New York Hospital and Cornell Medical Centre have identified by serological means a pair of factors, G and g in rabbits, strikingly similar in distribution, antibody formation and haemolytic power to the Rh-Hr system in man.

For details of the methods employed the reader is referred to the original article.

The same workers in the second paper report that they have been able to show that female rabbits may become immunized to one or other of the G-g blood group factors either following injection of suitable red cells or during pregnancy, and that the specific maternal antibodies cross the placenta and can affect the foetus *in utero*, with the production of typical haemolytic disease of the newborn. Female rabbits homozygous for the G factor in which no specific antibodies could be detected were mated with males bearing the g factor in their red cells, and others of type gg were mated with males bearing the G factor. The development of antibodies to G and to g was detected, and by means of Coombs' direct test the presence of coating antibody was demonstrated in the foetuses before suckling had occurred, showing that the antibodies had

crossed the placenta. Agglutinating antibodies were similarly demonstrated.

[These papers represent a step forward in the investigation of erythroblastosis foetalis. As yet, however, jaundice of the newborn and kernicterus have not been produced experimentally.]

J. C. McClure Browne

36. **Appendicitis in the Newborn: Case Report.**

By S. C. MEIGER and A. W. LUCAS. *Ann. Surg.*, **136**, 1044–1047, Dec. 1952. 7 refs.

A case is reported of a girl, the last of triplets, whose birth weight was 4 pounds 5 ounces. On the 10th day she cried out frequently and appeared to be in pain. Her stools were loose. She was cyanosed and showed marked dehydration. The abdomen was distended but was not rigid and no masses were felt. X-ray of the abdomen showed no evidence of obstruction. Laparotomy revealed an acutely inflamed appendix, the distal 1 cm. of which was covered by plastic exudate. Appendectomy was performed. A Meckel's diverticulum was also found and was removed. On the 4th postoperative day wound dehiscence and evisceration occurred. This was successfully repaired. Four days later the wound presented as a complete slough. This setback was overcome and the child made a complete recovery apart from a small incisional hernia.

Appendicitis in the newborn is extremely rare and is very different from that in the adult. Anatomically the appendix wall is thinner, allowing rupture to occur more readily. The omentum is small and thus does not form as good a barrier to spreading infection. Thirdly, the peritoneal cavity is smaller and generalized infection occurs earlier. Physiologically, in children the peritoneum absorbs toxins more rapidly and the water and electrolyte balance is more easily upset than in the adult. Clinically, the recognition of pain in the neonate may be very difficult and its location remains uncertain. Vomiting is an important symptom. The white blood count is often normal. Early diagnosis is all important and, when this is in doubt, repeated examinations at half-hour intervals are advised so that the trend of progress can be ascertained and early treatment instituted.

D. Q. Trounce

37. **Infection in the Newborn Baby.**

By A. MONCRIEFF. *Brit. med. J.*, 1–7, Jan. 3, 1953. 33 refs.

In his Charles West lecture at the Royal College of Physicians, the author stresses the high incidence of infection revealed by careful postmortem examination after neonatal death. He considers that difficulties in clinical diagnosis are associated with the erroneous beliefs that babies do not "catch" infections, such as the common cold, and that the normal rectal temperature in post-natal life is 99°F rather than the actual 97°F. Moreover, sometimes an overwhelming infection may cause a subnormal temperature before death.

Blood-borne infections acquired before birth include syphilis, tuberculosis, *Bact. coli* infections associated with maternal pyelitis, toxoplasmosis, and probably malaria. Of the virus infections, there are reports of the unborn child being affected by variola, vaccinia, herpes and "cytomegalic inclusion disease". The problem of hepatitis is a difficult one but there is evidence suggestive of transplacental infection.

During labour, or even in pregnancy, the infant may inhale infected material and at the time of delivery infection, particularly of the eyes, may be acquired from the mother's genital tract. An infected accoucheur may also be the agent.

In the human, it appears that passive immunity is transmitted at least mainly by the placenta. How quickly infants acquire active immunity is doubtful; it may be related to nutritional or genetic factors.

After birth, infection may gain entry via the respiratory tract, eyes, skin, alimentary tract or umbilicus. Usually there is only a local reaction at the primary focus but generalization may lead to toxaemia or septicaemia and, later, pyaemia. In the stage of generalization, the diagnosis may not be obvious, particularly if the primary focus has been missed.

Principles of treatment include careful correlation of chemotherapy and antibiotics with the bacteriological findings, continuation of breast feeding and the appropriate treatment of dehydration, anaemia and the local lesion.

Prevention of infection depends mainly on scrupulous nursing care. Aspiration of gastric contents in the premature baby is useful and the author is an "unrepentant believer" in soap and water for cleaning the skin. Prophylaxis also includes chemotherapy and antibiotics in prolonged labour. In the more speculative field, immunity to staphylococcal infection might be raised by the use of vaccines given to the mother and research should include investigation of nutritional factors and the possibility of increasing immunity by adding amino-acids to the diet of premature babies.

Doreen Daley

38. **Contribution to the Aetiology of Inheritable and Non-Inheritable Malformations.** (Beitrag zur erblichen und nichterblichen Missbildungsaetiologie.)

By H. GREBE and A. WINDORFER. *Dtsch. med. Wschr.*, **78**, 149–151, Jan. 30, 1953. 4 figs., 43 refs.

The authors stress the fact that congenital malformations must not be regarded as inherited and caused by a defect in the germinal plasma unless their familial occurrence is proved. Among the acquired causes for congenital malformations lack of oxygen in the early months of gestation ranks first. The type of the resulting abnormality depends on what stage of embryonal development has been reached when the oxygen deficiency occurs. It was shown experimentally that oxygen lack in 24-hours old chick embryos caused brain and spinal cord anomalies whereas limb hypoplasias resulted if the embryos were 36 hours old before oxygen was deprived. Other exogenous factors causing congenital malformations in animals are urethane, vitamin deficiencies, trypan blue, colchicine, insulin, boric acid, and pilocarpin.

The authors apply these experimental results to man and conclude that in the absence of a family history the aetiology of a given malformation may be either acquired or a mutation. Causes of acquired malfor-

mations are embryopathia, radiation damage, attempts at abortion with chemical agents, and trauma.

Four cases of similar malformations (2 familial and 2 alleged to be due to acquired causes) are discussed.

E. Wachtel

OBSTETRIC OPERATIONS

39. **Some Personal Considerations on the Technique of Internal Version.** (Algunas consideraciones personales y técnicas sobre la versión interna.)

By N. AMIGO DE BONET. *Toko-Ginec. Prát.*, **11**, 533–550, Dec. 1952.

The author reviews his personal experiences of internal version in the Clínica de la Residencia Maternal, Barcelona, before its cessation as an independent organization. During its existence this clinic dealt with some 300,000 abnormal obstetric cases. The writer proclaims himself an enthusiastic supporter of internal version, which he regards as one of the most satisfying obstetric procedures.

Historic references to internal version through the ages are given, dating back to the time of Hippocrates. Within comparatively more recent times, the author comments on the apparent popularity of this obstetric procedure during the 18th century, and of its dramatic decline in the following century.

Numerous statistics beginning in the early years of this century are given: those from three German clinics give an overall foetal mortality rate of 31.7 per cent for internal version, and the maternal mortality rate varies between 2 per cent and 4 per cent. In stating his own views the author maintains that internal version has a place in the management of slight cephalo-pelvic disproportion, providing that the soft tissues permit of the procedure. He also states that, in dealing with the undilated cervix, the greater the force employed for manual dilatation, the greater is the foetal mortality. He emphasizes that the cervix should be manually dilated slowly, and in every case where internal version has been performed the cervix should be inspected afterwards. The author then presents his own series, consisting of 287 cases of internal version. There were no maternal deaths and only 6 foetal deaths—including 1 due to erythroblastosis foetalis and another of foetal death *in utero*.

In this series the cervix in 87 cases was fully dilated at the time of version, whilst in 179 cases that stage had not been reached.

Among the remainder, in 18 cases labour had been induced [method not stated] including 5 cases of previous Caesarean section, and there were 3 cases of placenta praevia—2 marginal and 1 central.

In conclusion, the author expresses his belief in internal version as the procedure to be practised in the art of obstetrics, rather than the modern tendency to employ the surgical operation of Caesarean section.

John F. Foulkes

40. **Scars of the Pregnant and Non-pregnant Uterus. Histologic Comparison of Scars Two Weeks Post-operatively.**

By I. SIEGEL. *Amer. J. Obstet. Gynec.*, **64**, 301–308, Aug. 1952. 8 figs., 31 refs.

It is at the present time generally believed that Caesarean section incisions in the uterus heal by formation of connective tissue only, rather than by regeneration of muscle fibres, and that myomectomy incisions in the non-pregnant uterus heal better than incisions in the pregnant uterus chiefly because the non-pregnant uterus is at rest during healing. The author has made incisions into the uterine horns in non-pregnant and in pregnant dogs and compared the scars in each. He found that both healed by formation of connective tissue only, and that they differed only in the amount of connective tissue present in the scar. In the non-pregnant uterus the scar was thinner and contained much less connective tissue than the pregnant uterus. He therefore considers that the post-myomectomy scar should be given consideration equal to that given to the post-Caesarean section scar in so far as the risks of rupture in subsequent pregnancy and labour are concerned.

F. J. Browne

MATERNAL MORBIDITY AND MORTALITY

41. **Postpartum Anal Fissure.**

By J. D. MARTIN. *Lancet*, **1**, 271–273, Feb. 7, 1953. 9 refs.

Attention is drawn to the common occurrence of anal fissure causing symptoms in postpartum women. Of 424 patients seen 6 weeks after delivery 50 complained of anal symptoms. The symptoms were due to haemorrhoids in 5 and anal fissure in the remaining 45. The fissures were single in 24 patients and multiple in the remaining 21. The onset of symptoms usually occurred within 14 days of delivery. It is maintained that the cause of the fissure is the trauma of vaginal delivery; that the more traumatic the delivery the more likely is a fissure to be produced; and that consequently the fissure is more common in the primiparous patient. The point is made that, whereas the haemorrhoid produces symptoms in the lying-in period and usually undergoes spontaneous cure within 6 weeks of delivery, the fissure, owing to the laxity of the anal sphincter and the presence of wounds of the perineum, usually produces symptoms after the lying-in period. Avoidance of constipation, care in the use of enema syringes, avoidance of damage to the anal margin by tears, and timely episiotomy will do much to lessen the production of the fissure. Conservative treatment consisting of the application of an anaesthetizing ointment prior to defaecation or gentle stretching of the anal sphincter was successful in all the patients under review.

H. H. Fouracre Barns

42. **Fatal Emboli in the clinic of Obstetrics and Gynaecology at the Medical Academy in Wroclaw in the Years 1945–1951.** (Smiertelne zatory w i klinice położniciwa i chorob kobiecych we Wroclawiu w latach 1945–1951.)

By M. MEDYNSKY. *Ginec. Polska*, **23**, 351–358, July-Oct. 1952. 8 refs.

The author describes 4 cases of fatal embolism which occurred during 6 years in the Women's Hospital in Wroclaw. Of these, 3 were thrombolitic emboli, and 1 an air embolus. This last occurred on the table while the abdomen was being closed after a Caesarean section. The frequency of fatal emboli in the whole series amounts to 0.05 per cent. The cases are described in detail, and the conclusion reached is that, if such factors as low haemoglobin, slow pulse and peripheral stagnation can be avoided, a reduction of fatal emboli from 1 in 1,500 to 1 in 3,000 confinements was achieved. Early ambulation is advocated.

S. H. Riterband

GYNAECOLOGY

GENERAL

43. **Two Rare Clinical Cases.** (Dos casos clinicos poco frecuentes.)

By J. PALLARES CACHA. *Toko-Ginec. práct.*, **11**, 551–554. Dec. 1952.

The author reports 2 cases of clinical interest.

1. A patient aged 32 years, para 3 plus 2, in her 4th month of pregnancy, complained of continuous urinary incontinence, which had been preceded by retention.

Her general state of health was poor, and on abdominal palpation a tender mass rising out of the pelvis to the level of the umbilicus was found, as well as oedema of the lower abdominal wall. Vaginal examination revealed a fullness in the posterior wall, which when pressed upon caused urine to escape from the urinary meatus.

Catheterization produced 2,250 ml. of urine. The diagnosis of a retroverted gravid uterus was made. The uterus was thereupon anteverted manually.

When seen 5 weeks later, she was symptom free and the pregnancy was progressing normally.

2. The author was called to a village where a patient aged 60 years was suffering from severe vaginal haemorrhage. She gave a history of bleeding 11 years previously which was stated to be due to a tumour, for which she had refused operation. For the past 3 months, she had been conscious of a mass intermittently protruding through the vulva and, during the past 4 weeks, this tumour had been continually outside the vulva. On examination, a mass about the size of a fist was found outside the vulval orifice, and it was attached by a pedicle (pedunculated fibromyoma) to another mass above.

Careful investigation revealed the upper mass to be an inverted uterus, on one side of which the tubal orifice could be seen, and at the corresponding site on the opposite side was the pedicle, which was showing signs of strangulation.

The abdominal cavity was opened and from above could be seen the cavity in the pelvis through which the inverted uterus had passed, and the Fallopian tubes were now passing. The vesical peritoneum was wine coloured and the adjacent vessels very dilated. On digital palpation, the opening was rigid and undilatable.

A subtotal hysterectomy was performed [technique not described]. The patient was discharged from hospital 7 days later.

John F. Foulkes

44. **Leukoplakia of the Vulva.**

By N. F. MILLER, G. M. RILEY, and M. STANLEY. *Amer. J. Obstet. Gynec.*, **64**, 768–779, Oct. 1952. 12 figs., 19 refs.

The authors reject the vitamin A deficiency theory of the aetiology of leukoplakia for 3 reasons: (a) they have not found any deficiency of blood plasma vitamin A or any consistent deficiency of gastric hydrochloric acid, (*b*) leukoplakia is not common in women with pernicious anaemia who always have achlorhydria, (*c*) they have not found any benefit from the therapeutic use of vitamin A and hydrochloric acid. The same is true of vitamin C. In an attempt to find some chronic irritative factor the urines of several leukoplakic patients were analyzed. The only difference found was in the amount of total organic acids of endogenous and exogenous origin which were significantly increased as compared with controls.

F. J. Browne

FUNCTIONAL DISORDERS

45. **The Empiric Usage of Low-dosage Irradiation in Amenorrhea.**

By S. L. ISRAEL. *Amer. J. Obstet. Gynec.*, **64**, 971–987, Nov. 1952. 1 fig. 40 refs.

This paper is concerned with the analysis of the results in 124 patients with secondary amenorrhoea or oligomenorrhoea treated during the 15-year period 1936–1950. The term "amenorrhoea" is employed when the interval between periods is 4 or more months, and "oligomenorrhoea" when the menstrual intervals are less than 4 months. The following are regarded as contra-indications to treatment: previous unilateral oöphorectomy, immature ovaries, and the possibility of early pregnancy. Both pituitary and ovaries are irradiated at each of 3 sittings one week apart, the dose being from 80 to 100 r each week to both the pituitary and ovarian fields. For various reasons such as failure to stay the course, incomplete follow-up, or antecedent adjunctive therapy such as dilatation and curettage or cyclical steroidal therapy, 34 of the 124 patients were excluded in analyzing the results. Cure was considered to have taken place if menstruation was regularly cyclic and pregnancy occurred before the end of a year. "Improved" patients were those whose menstrual intervals were reduced to at least half their pretreatment length.

Using these criteria, of 61 patients with oligomenorrhoea, 80 per cent were cured, 3 per cent were improved, and 16 per cent were failures; of the 29 cases of secondary amenorrhoea, 52 per cent were cured, 10 per cent improved, and 38 per cent failures. Twenty-seven of the 90 patients became pregnant within one year following treatment, and of these 23 gave birth to normal children at term. Three of the 27 pregnancies began without an intervening period, illustrating the importance of examining patients who do not menstruate within several months of treatment.

There were 2 abortions, 1 ectopic pregnancy, and 1 microcephalic baby which was conceived during the course of the X-ray treatment. This patient has since had 2 normal children.

[These results are not impressive and one wonders whether spontaneous cure might not have occurred in as large a percentage of cases without treatment at all. The danger of irradiation of an early ovum is a very real one and might be quite difficult to avoid.]

F. J. Browne

46. **Acute Appendicitis during Menstruation.**

By A. A. LEVY. *New Engl. J. Med.*, **247**, 350–352, Sept. 4, 1952. 1 ref.

The author confesses to an impression that acute appendicitis rarely occurs during menstruation and he brings figures to support his contention. Out of 242 female patients between the ages of 11 and 50 operated upon for acute appendicitis, only 9 were menstruating and not one was in her first or second menstrual day. Out of another 460 patients in whom appendicitis was diagnosed but not confirmed at operation, 15 were menstruating. The author concludes ". . . nearly two-thirds of patients admitted during a period with a diagnosis of acute appendicitis and operated upon did not have acute appendicitis." [This is precisely the same as the proportion for the entire series.]

A plea is made for the avoidance of emergency operation for appendicectomy during the menstrual period, and for the consideration of other pathology that might be responsible for symptoms, so that adequate surgery may later be performed through an adequate incision. No argument is propounded as to why acute appendicitis should not occur during the early days of a menstrual period. *W. G. Mills*

47. **The Combined Use of Three Hormones in the Treatment of Functional Uterine Haemorrhage.** (L'associazione triormonale nella terapia delle emorragie uterine funzionali.)

By G. PESCETTO. *Minerva ginec.*, **4**, 344–348, Aug. 1952. 11 refs.

The author advocates the use of both ovarian hormones together with male hormone on the following grounds: Progesterone facilitates the metabolism of oestradiol and oestriol towards oestrone, and also favours the complete desquamation of the endometrium, a " medical " curettage being achieved. Testosterone is able to neutralize the action of oestrogens on the endometrium, inhibits the F.S.H. gonadotrophins of the pituitary gland, and stimulates growth and tonicity of the myometrium.

The author values the suggestions of Greenblatt (*Med. Clin. N. Amer.*, **34**, 1551, 1950) who has experimented with preparations containing 10,000 i.u. of oestroform benzoate, 25 mg. of progesterone, and 25 mg. of testosterone propionate for 3 to 5 days consecutively by injection. Greenblatt claims arrest of haemorrhage in functional uterine bleeding within 6 to 24 hours. Recently, Greenblatt has had good results with 4 consecutive days' treatment with 25 mg. of progesterone, 25 mg. of testosterone, and 1 mg. of oestradiol propionate.

The author gives details of 12 cases in which he uses a preparation containing 1.5 mg. of oestroform propionate, 12.5 mg. of progesterone, and 25 mg. of testosterone propionate. The cases were assessed as regards clinical symptoms and by examining basal temperature charts, vaginal smears, and endometrial biopsies. The author recommends the use of this trihormonal preparation in types of excessive uterine haemorrhage of purely functional origin, there being no evidence of organic abnormality of the reproductive system, and in which biopsy of the endometrium definitely establishes evidence of hyperoestrogenism.

The results from the use of this preparation, when there is evidence of associated pathology, are not good.

The author suggests 5 daily injections, which total 125 mg. testosterone propionate, 62.5 mg. progesterone, and 7.5 mg. of oestradiol propionate. He claims arrest of haemorrhage in 12 to 72 hours. Arrest of the haemorrhage is followed, usually, by freedom from loss for at least 3 weeks and, if a further excessive haemorrhage occurs, the course can be repeated, but probably in reduced dosage.

The author believes that success of the treatment is due to inhibition of the secretion of the pituitary gonadotrophins, together with the tonic effect on the uterine muscle, and the medical curettage produced by progesterone. He also believes that the small dose of oestradiol propionate is sufficient to neutralize any of the secondary effects of testosterone towards masculinization, particularly in young patients.

Patrick Steptoe

48. **Haematometra Following Depot-Oestromon.** (Haematometra nach Depot-Oestromon.)

By W. v. HOEGEN. *Die Medizinische*, 124–126, Jan. 24, 1953.

Dr. Hoegen warns against the uncritical use of oestrogenic substances in the menopause as they act on the endometrium and may cause severe uterine haemorrhages. He records the case of a woman aged 59, 5 years postmenopausal, who received 4 slow acting oestrogen injections at 7 to 14 days' intervals. Five weeks after the last injection she complained of severe abdominal pains and was found to have a large fluctuating tumour in the vagina. This proved to be due to ballooning of the cervix filled with large masses of blood which were evacuated. The curetting showed metropathia cystica. The haematometra was due to a previously acquired stenosis of the external os.

Hormone therapy should be reserved for women with severe menopausal symptoms refractory to other therapeutical measures. Oestrogens given orally are, according to Hoegen, not very effective and single injections of oily suspensions seem uneconomic as 85 per cent of the active principle is excreted in the urine.

Three methods of administration appear rational: (1) implantation of solid crystals, (2) injection of crystal suspensions, (3) preparations of oily stilboestroldimethyl ether which are very slowly absorbed (depot oestromon, depot cyren). Crystals should only be given to women after total or subtotal hysterectomy since they carry the danger of prolonged uterine

haemorrhage. Crystal suspensions of 10 mg. oestradiol monobenzoate are effective for 1 to 2 months and carry little risk of bleeding. Hoegen favours the third group of preparations though, as the case record shows, caution is also advisable. The question of dosage is difficult and has to be adjusted according to the individual requirements of each woman. It is suggested to give an initial depot of 12 mg. (2 ml.) and wait for 6 to 8 days. If no relief is obtained the injection should be repeated until a total of 3 is reached.

E. Wachtel

49. **The Female Factor in Fertility and Infertility. I. Effects of Delayed Fertilization on the Development of the Pronuclei in Rat Ova.**

By R. J. BLANDAU. *Fertil. Steril.*, **3**, 349–365, Sept.-Oct. 1952. 26 figs., 18 refs.

In a study of 40 female rats ovulation, as evidenced by the finding of ruptured follicles, took place between 9 and 11 hours after the onset of heat. Bearing this in mind, 78 rats were artificially inseminated as follows: (*a*) 13 during heat, (*b*) 18 3 to 5 hours after ovulation, (*c*) 15 6 to 8 hours after ovulation, (*d*) 32 9 to 12 hours after ovulation. Details of recovery of the ova are given and ova were then stained and examined microscopically. In (*a*) 98.6 per cent appeared satisfactorily fertilized and only 2 ova showed abnormalities of the pronucleus. In (*b*) there were 96.1 per cent fertilized and 8 abnormal ova (3.96 per cent), in (*c*) 86 per cent fertilized and 14 per cent abnormal ova. In (*d*) only 57 per cent fertilized and 47.8 per cent ova showed abnormalities. Abnormalities were chiefly in the form of failure of development and fragmentation of female pronucleus and the incidence of this increases with the age of ovum at fertilization. The male pronucleus frequently develops normally even to the formation of a metaphase plate though there is no evidence that it can divide into blastomeres, although the author thinks this is likely. Failure of fertilization in (*d*) was due to failure of sperm to penetrate the zona pellucida. This, in rats, could not be correlated with any change in the conditions of the granulosa cells.

D. M. Sheppard

INFECTIONS OF THE REPRODUCTIVE ORGANS

50. **The X-ray Picture of Uterine and Tubal Tuberculosis.**

By J. MARŠÁLEK. *Gynaecologia, Basle*, **135**, 37–44, Jan. 1953.

Hysterosalpingography can be used in the diagnosis of uterine and tubal tuberculosis. In performing the investigation certain points are of importance. The uterus must be filled under visual control by screening. A preliminary X-ray is taken to look for calcified lymph nodes in the pelvis. A stereoscopic picture is taken of the uterus to show endometrial changes. The contrast material must be free of air bubbles; oily solutions are more suitable for this reason. The solution must be injected under low pressure to avoid the risk of disseminating the infection.

In uterine tuberculosis the cavity of the uterus presents round or oval clear spaces and the fundal shadow is uneven.

Three main changes are seen in tuberculous tubes. In the first, destructive changes take place in the mucous and muscular coats: the shadow shows fistulae penetrating into the uterine wall, the ampullary end is closed. In the second type, the tubes are thick and rigid, the tube appearing straight and "like a policeman's baton". In the third type, filling is uneven with beading of the lumen like a rosary. The ampulla is closed.

Josephine Barnes

51. **Functional Activity of the Tuberculous Endometrium.** (Über die Schleimhautfunktion bei Endometriumtuberkulose.)

By J. NEVINNY-STICKEL. *Arch. Gynäk.*, **182**, 104–124, 1925. 8 figs., bibliography.

This is a report on 53 cases of endometrial tuberculosis which were studied at the Department of Pathology of Hamburg-Altona General Hospital during the last 12 years. Forty-six of the 53 specimens were obtained (either by curettage or by hysterectomy) from patients of child-bearing age, the maximum incidence being in the age group 20 to 24. Out of these 46 cases the endometrium showed signs of cyclical activity in 33 instances. In 20 cases of the latter group there was evidence of incomplete shedding of the endometrium; this is explained by the presence of dense connective tissue in the tuberculous endometrium. This incomplete shedding is thought to be responsible both for the rarity of spontaneous cure of tuberculous endometritis and for the menstrual anomalies (menorrhagia, metrorrhagia) and the dysmenorrhoea observed in patients suffering from tuberculous endometritis. In the remaining 13 specimens obtained from patients of child-bearing age the endometrium showed no cyclical changes and is described as functionless.

N. Alders

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

52. **The Control of Inoperable Genital Carcinoma by Heterosexual Hormone Therapy.** (Kontrollmöglichkeiten kontrasexueller Hormontherapie bei inoperablen Genitalkarzinomen.)

By H. TISCHER. *Krebsarzt*, **7**, 224–230, Aug. 1, 1952. 2 figs., 12 refs.

Working at the Second Obstetric-Gynaecological Clinic of Vienna University, the author has studied the question of dosage in the treatment of inoperable genital carcinoma with heterosexual hormones. The doses recommended by Vasterling (50 mg. of testosterone in oily solution injected intramuscularly daily for 3 weeks, every other day for another 3 weeks, and then twice weekly) are considered to be unnecessarily high because, as soon as a high blood-concentration of androgens is reached, further high doses are simply excreted. The author recommended daily intramuscular injection of "perandren", 50 mg. for 7 days, followed by a daily dose of 25 mg. for several weeks until a total of 2,000 mg. has been given; after that a

"maintenance dose" of 50 mg. should be injected twice weekly.

Neither regular estimation of the excretion of 17-ketosteroids nor examination of vaginal smears has been found reliable for the assessment of the suitability of the doses of testosterone administered.

N. Alders

53. **Relations between Hormone-secreting Tumours and Adenocarcinoma of the Uterine Body.** (Beziehungen zwischen hormonbildenden Tumoren und Carcinoma adenomatosum corporis uteri.)

By H. G. Müller. *Z. Geburtsh. Gynäk.*, **137**, 126–137, 1952. 8 figs., 5 refs.

In a previous paper the author stated that he believed that, in a climacterium with hormonal disturbances due to the presence of a feminizing ovarian tumour, there was produced a local predisposition to adenocarcinoma of the body of the uterus. Since this original paper the author has observed 4 patients with granulosa-cell tumours; 3 of the 4 patients had adenocarcinoma of the body of the uterus and the 4th had cystic glandular hyperplasia of the endometrium with atypical cells and nuclei. The author postulates that the follicular hormone produced by these tumours may have a cancer-inducing substance, which acts on specific organs or tissues at an age when carcinoma commonly occurs.

Dr. Müller investigated the ovaries of 80 foetuses and new born infants and found granulosa cells present in the foetuses but rarely in the infants: he also examined 100 ovaries obtained from adults at operation and never found granulosa-cell "rests". He points out that granulosa-cell tumours are usually met with at an age when follicle ripening, and therefore granulosa-cell proliferation, rarely occurs. These facts have led the author to conclude that granulosa-cell tumours originate not in redundant granulosa cells but from cells of the early ovarian mesenchyme. The hormone which they produce may therefore differ from that of the ovarian follicle and may have the power of inducing tumour formation.

Gladys Dodds

54. **New Facts Concerning Post-molar Malignant Chorion Epithelioma.** (Faits nouveaux concernant le chorio-epithéliome malin post-molaire.)

By H. Hinglais, and M. Hinglais. *Presse méd.*, **60**, 1359–1361, Oct. 11, 1952. 2 refs.

The authors reject the view that malignant chorion-epithelioma occurs in a primary phase when it is restricted to the uterus, and in a secondary when there is generalized metastasis. They believe that the condition is, from the first, widespread, with metastases throughout the body, and that, if the primary focus is removed by hysterectomy at a sufficiently early stage, spontaneous regression of the metastases will occur. They have studied by means of serial biological tests a series of 16 cases all proved histologically to be malignant. The presence of prolan B is measurable evidence of trophoblastic activity and can be estimated biologically. Even in the cases operated upon earliest in the present series, prolan B could be demonstrated for 2 weeks to 4 months after extirpation of the primary growth. It was considered that in all cases this was derived from metastases. Serial estimations have shown in almost all cases a progressive fall in the titre of prolan B, although 1 case showed an initial rise in titre 8 weeks after hysterectomy. They believe that the biological test may indicate the presence of metastasis, even where there is no clinical evidence of any such lesion.

The regression of the metastases is considered to be the result of a struggle between the defence mechanisms of the body and the activity of the neoplasm, and they point out that the metastases, if already too far advanced, will overcome the defences and make progress. The presence of widespread metastasis should not be regarded as a contra-indication to removal of the uterus. Finally, the authors distinguish between chorionepithelioma occurring in a teratoma whose metastases do not respond by regression as described above, and the post-molar chorionepithelioma with which this paper is concerned. The former is a cancer absolutely different from all others in that it is not homogenetic with its host organism, but is derived essentially from another individual. It is suggested that further study along these lines may reveal interesting facts with regard to the body's defence against other types of cancer.

J. A. Chalmers

55. **Primary Carcinoma of the Vagina.**

By I. H. Kaiser. *Cancer*, **5**, 1146–1160, Nov. 1952. 17 tables, 15 refs.

The paper fully analyzes 55 cases of primary carcinoma of the vagina seen at the University of Minnesota between 1927 and 1950. Records prior to 1927 were found to be insufficient to warrant the inclusion of cases seen before that date. Every patient has been followed until death or until December 31st, 1951.

The absolute 5-year cure rate is based on 38 patients who were seen prior to 1946. The overall absolute survival rate for this clinic is 13 per cent; the relative 5-year cure rate is 15 per cent. There were 49 squamous-cell carcinomas and 6 adenocarcinomas.

Thirty-eight of the 55 patients complained of either vaginal bleeding or some form of vaginal discharge. Three patients had no symptoms at all. In 15 cases the duration of symptoms was 3 months or less—4 of these were untreatable. In 9 cases the duration of symptoms was 13 months or more and 5 were treated.

With regard to age incidence the decade most favoured in these cases was 60 to 69 in which 18 of the 55 cases occurred. Altogether 28 tumours occurred in women under 60, and 27 in women over 60.

Thirty-two of the 55 patients had some form of complicating disease on admission of which hypertension (14 cases) was the most common. A history of vaginal trauma was present in 9 cases, 5 of which had prolapse and 3 others had worn pessaries.

The majority of the tumours (27) involved the posterior wall.

The author explains that since routine dissection of the inguinal lymph nodes was not done the incidence of inguinal node metastases is not known, but in cases

in which this was done no inguinal node metastases were found in tumours limited to the upper third of the vagina. Continuous spread of the tumour to the parametria was found in 23 cases; to the bladder in 3, to the recto-vaginal septum in 2; to the labia in 5, and to the cervix in 2. Lung metastases were present in 1 case.

Six cases were treated by surgery. Hysterectomy and vaginectomy was carried out in 2, one of whom died of aplastic anaemia after X-ray therapy and one of whom died of recurrence. Vaginal hysterectomy and vaginectomy was done once and the patient died 8 months later of ureteral obstruction. Hysterectomy, vaginectomy, and resection of rectum was carried out in 2, one of whom died of leukopenia following operation. The other is living at 10 years and 7 months from the time of treatment. The sixth case was treated by hysterectomy, vaginectomy, and cystectomy and died with a pelvic recurrence 6 months later.

Irradiation therapy was used in 41 cases. This consisted of X-rays and radium in 27; X-rays and radon in 6; X-rays, radium, and radon in 1; X-rays alone in 3; radium and radon in 2; radium alone and radon alone, 1 each.

Twenty-three cases developed complications of irradiation therapy: irradiation ulcer in 7; vulvitis in 6; urinary tract infection in 4; severe leukopenia in 2; fracture of femur in 2; and "severe reactions causing interruption of therapy" in 2.

Prior to 1944 X-ray therapy was by 200 kV. machine with a half-value layer equal to 1.4 mm. of copper at a focal skin distance of 60 to 70 cm. Large anterior pelvic fields 18 × 20 cm. were used and slightly smaller fields in the lateral, posterior oblique, and anterior oblique regions. The full daily dose was 300 to 400 r in air and the total depth dose to the centre of the pelvis was 3,000 r.

Since 1944 a 400 kV. machine has been used with a half-value layer of 3.9 mm. of copper at a focal skin distance of 70 to 80 cm. The 2 anterior oblique fields have been omitted. The total dosage is 3,000 r in 28 days.

The radium techniques used were: (1) For lesions restricted to the upper third of the vagina, an arrangement similar to that used for treating carcinoma of the cervix, and (2) for lower lesions radium introduced into dental wax moulds. The dose aimed at has been 7,000 r to the farthest point at the depth of the tumour.

Of the 8 fistulas seen 3 were present on admission and 5 occurred after treatment. Of these 5, 4 were thought to be due to tumour and only 1 due to treatment. Three were recto-vaginal and 1 vesico-vaginal and 1 urethrovaginal.

The 5-year survival rate of cases treated by irradiation is 11 per cent.

Of the 46 cases who have so far died in this series, in 39 the cause of death was accredited to tumour; persistence of tumour in the treated area in 20; recurrent tumour in 5; metastasic tumour in 2; deaths due to therapy in 2; whilst no definite diagnosis was obtainable in 10. Seven cases died of intercurrent disease, 3 of which were due to carcinoma in other sites, all proven by autopsy (one lymphosarcoma of the caecum; 1 carcinoma of the stomach; 1 carcinoma of the gallbladder). Of the 6 adenocarcinomas only 3 were treated and none survived 5 years.

In the discussion the author stresses the rarity of the lesion and the lack of opportunity that most people have of studying this disease and he quotes at length reports by Livingston from the Memorial Hospital, New York, of 110 cases and and Huber from the Women's Clinic at Kiel on 152 cases. He suggests that improvement in the results can only come from an integration of the known biology of the disease with the capacities of the therapeutic weapons at our disposal.

He believes that improved irradiation will do much to improve the results of the tumours in the upper vagina but that in the lower vagina the inguinal metastases are a serious and important factor and that one of the first steps towards cure in this type of lesion is an all out radical attack on the inguinal lymph nodes, combined with, if necessary, hysterectomy and vaginectomy and vulvectomy. In appropriate patients resection of the bladder, rectum, and vagina may be indicated but he points out that its applicability is low and mortality high but it can be discussed because in this particular group the salvage in the past has been very close to nil, and he concludes by pointing out that in the past 25 years there has been gradual improvement in therapy in carcinoma of the cervix and vulva but not in carcinoma of the vagina, but with a bold application of the maximum resources of both radium and surgery combined it seems reasonable to expect that carcinoma of the vagina will yield an increasing survival rate.

[This is a long and important contribution to the study of a rare and lethal disease. It is a frank exposition of the cases which have been seen in the author's clinic. They have been subjected to the most careful analysis and the information which results from this study is of the greatest value.

In one respect the abstracter finds himself in disagreement with the author and that is in relation to his somewhat optimistic view of the future use of radiotherapy. There is little doubt that the latter cases treated at Minnesota with radiotherapy have received treatment which is adequate from the technical standpoint, so adequate in fact that the complications of therapy are very much greater than one would expect to see in an English clinic, yet the survival rate is no better; in fact it is worse than we have obtained in the Newcastle centre, with much less dosage and with many fewer complications. Our recent, and as yet unpublished, studies on the behaviour of vaginal tumours during irradiation have shown that the majority do not respond to radiation therapy even if it is adequately given.

The difficulties of surgical treatment which the author enumerates are in full agreement with our experiences in this centre, for anything short of a total pelvic clearance seems doomed to failure and with a high incidence of node metastases even total pelvic clearance cannot be expected to be startingly

successful. Furthermore, since a large number of these patients are in the advanced age groups such radical surgery will be limited in its application as the author points out.

The author supports my own plea for concentrating these cases in special clinics and so rare is the disease that unless this is done we cannot hope to achieve any progress in the treatment of this, probably the most stubborn of genital tract carcinomas.

This paper is an extremely valuable contribution to the subject and should certainly be read by all who are interested in carcinoma of the vagina.]

Stanley Way

56. **Possible Modes of Action of Testosterone in Carcinoma of the Uterus.** (Wirkungsmöglichkeiten des Testosterons beim Uteruskarzinom.)

By H. HUSSLEIN. *Krebsarzt*, **7**, 219—223, Aug. 1, 1952. 12 refs.

The encouraging results of heterosexual hormone therapy in cases of cancer of the prostate and of the breast have led to the exhibition of testosterone in cases of uterine carcinoma. The possible modes of action of testosterones are discussed. (1) So-called anti-oestrogenic action. Oestrogens and testosterones are by no means absolute antagonists. Both suppress the anterior pituitary, and the so-called anti-oestrogenic action of testosterone is actually (2) anti-gonadotrophic. Experimental evidence as to the influence of gonadotrophic hormones on the growth of genital cancer is as yet conflicting. (3) Anti-carcinogenic action. While there is clinical evidence that bone metastases of breast cancer have disappeared with the exhibition of testosterone, nothing definite is known about a possible cytostatic action of this substance on the cancer cell. (4) Vasoconstriction of myometrial vessels. This effect of testosterone, first described by Abarbanel, may be responsible for the inhibition of growth of uterine cancer. (5) Psychological effect. The author has been impressed by the euphoric action of testosterone. (6) General anabolic effect. This is probably the most important factor in the improvement of general health of cancer patients treated with testosterone.

N. Alders

57. **Recent Concepts on the Diagnosis and Management of Uterine Cancer.** (Conceptions actuelles sur le diagnostic et le traitement du cancer de l'uterus.)

By G. TESAURO. *Brux. Méd.*, **5**, 221–245, Feb. 1, 1953. 16 figs., 165 refs.

Statistics of the World Health Organisation show that of 100 women presenting with cancer of the cervix, 55 are quite inoperable.

The history of the methods of treatment of cervical carcinoma is briefly reviewed.

The writer, working in the Department of Obstetrics and Gynaecology of the University of Naples, uses as his method of treatment Wertheim's hysterectomy followed by X-rays, according to the Schaeffer-Witte technique. From 1947–52, there were 75 cases of carcinoma of the cervix. Forty-five were considered operable, and the above method was carried out. There was a primary mortality of 1 (2.2 per cent) and the rest are still surviving, 2 for 5 years, 4 for 4 years, 7 for 3 years, 4 for 2 years, and 27 for 1 year. The 30 inoperable cases were treated by radium and X-rays with a 50 per cent mortality during the period under review.

As regards treatment of carcinoma of the uterine body, there is a general agreement that surgery combined with radiotherapy gives the best results (75 per cent as against 68 per cent for surgery alone, and 38 per cent for irradiation alone).

Carcinoma *in situ* is treated by total hysterectomy. As regards the early diagnosis of carcinoma of the uterus, the writer uses the vaginal smear routinely as as diagnostic aid, but emphasizes that this does not obviate careful examination and biopsy. Other methods of early diagnosis (colpomicroscopy and the phase contrast method) are briefly discussed.

J. C. McClure Browne

58. **A Twenty-five Year Evaluation of the Treatment ment of Carcinoma of the Cervix with Irradiation.**

By L. C. SCHEFFEY, W. J. THUDIUM, D. M. FARRELL, G. A. HAHN, and W. R. LANG. *Amer. J. Obstet. Gynec.*, **64**, 233–247, Aug. 1952. 22 refs.

This report from the Jefferson Medical College Hospital, Philadelphia, gives the results in 485 patients seen and/or treated from 1921 to 1946. Only 8 of the 485 patients are untraced and of these 4 were followed from 8 to 18 years before they were lost. The follow-up figure is therefore 98.5 per cent. Twenty-seven per cent of the cases were in women of 40 years and under; the youngest patient was 22 months and the oldest 79 years of age. The incidence of adenocarcinoma was 5.7 per cent, the remainder being squamous-cell cancer. During the same period there were 77 cases of endometrial cancer so that cancer of the cervix occurred 6.3 times as often as cancer of the corpus.

There were in the series 73 cases of stage I cancer, the absolute 5-year survival rate being 54.7 per cent, there were 275 cases of stage II cancer with an absolute 5-year survival rate of 32.7 per cent; 89 cases of stage III, the absolute survival rate being 4.5, while among 48 stage IV cases there were no 5-year survivals. The total survival rate among the 485 cases was 27.6 per cent. There were 21 cases of cancer of the cervical stump with a 5-year survival rate of 48 per cent. Improvements in methods of irradiation during the 25 years have been reflected in improved results. Thus in the years 1921–1936 the 5-year survival rate was only 27.9 per cent; in the years 1936–1942 it was 34.6 per cent, and from 1942–1946 it was 47.6 per cent.

F. J. Browne

59. **A Debate. What is Cancer in situ of the Cervix? Is it the Preinvasive Form of True Carcinoma?**

By A. T. HERTIG and P. A. YOUNGE. *Amer. J. Obstet. Gynec.*, **64**, 807–815, Oct. 1952. 3 figs., 15 refs.

Carcinoma in situ of the Cervix: A General Consideration.

By J. L. MCKELVEY. *Amer. J. Obstet. Gynec.*, **64**, 816–832, Oct. 1952. 10 figs., 2 refs.

The Methods of Management of Carcinoma in situ of the Cervix.

By B. Carter, K. Cuyler, W. L. Thomas, R. Creadick, and R. Alter. *Amer. J. Obstet. Gynec.*, **64**, 833–849, Oct. 1952.

These 3 papers occupy some 50 pages and may be considered together. They are worth reading in full if only to show how much the whole subject of cancer of the cervix *in situ* is still in the melting pot—terminology, diagnosis, and treatment. Hertig concludes that it is the preinvasive stage of squamous carcinoma of the cervix and that it takes from 1 to 13 years for the *in situ* stage to go on to true carcinoma, but whether all cases if left alone would eventually become invasive is not known. There was little agreement on diagnosis except on its difficulty. Novak for instance, would confine it to cases in which the entire thickness of the epidermis is replaced by cells that are morphologically indistinguishable from those of frank invasive carcinoma with complete loss of stratification but no penetration beyond the basement membrane. McKelvey, on the other hand, objects to the concept that the malignant changes must involve the whole depth of the epithelium and considers that a diagnosis of malignancy is justified even when they are confined to the basal layer which spreads at its margin and replaces the normal basal layer at the point of contact. Lesions showing this early epithelial pattern have been followed without treatment and shown to progress slowly to clinical cancer. Hyperplastic lesions of the cervix epithelium, including atypical forms of erosion healing, and the so-called basal hyperplasia must be distinguished from malignancy. If in doubt the patient should be watched with repeated biopsies and the very occasional radical removal of a uterus when this method is inconclusive. Great care should be exercised in labelling a case "cancer *in situ*" for the patient is presented with a life-long fear which may be unjustified and unnecessary. Te Linde in debatable cases does a sharp conization of the cervix and cuts many blocks from the tissues. *F. J. Browne*

60. **Recurrence of Tumour after Total Hysterectomy for Carcinoma in situ.**

By J. B. Graham and J. V. Meigs. *Amer. J. Obstet. Gynec.*, **64**, 1159–1162, Nov. 1952. 5 figs., 8 refs.

Total hysterectomy is usually regarded as a certain cure for cancer *in situ* of the cervix but several cases have now been reported in which it did not prevent the development of invasive cancer, sometimes years later. The authors report 3 examples of this, though in 2 of them the only evidence of the invasive cancer was a positive vaginal smear. In the third case a malignant nodule was found in the vaginal apex 8 years after the total hysterectomy. The authors think that the most likely explanation is that the cancer *in situ* extended out on to the vaginal wall at the time of operation and subsequently became invasive.

[These reports of the late recurrence of cancer after total hysterectomy for cancer *in situ* of the cervix are disconcerting, and emphasize the importance (which the authors do) of a long follow-up of all cases. They make one wonder too whether a better treatment than total hysterectomy would not be to give radium up to the full therapeutic dose for cancer of the cervix, and follow it, say 6 weeks later, by total hysterectomy. The cases also emphasize the importance of removing a generous cuff of vagina at the operation.] *F. J. Browne*

61. **The Effect of Pre-operative Radiation of Adenocarcinoma of the Endometrium.**

By H. E. Schmitz, C. J. Smith, and C. J. Gajewski. *Amer. J. Obstet. Gynec.*, **64**, 952–970, Nov. 1952. 15 figs., 16 refs.

Whether pre-operative radiation improves the results in endometrial cancer is still questionable. It has been claimed for it that it damages cancer cells to a point beyond which the manipulations at the subsequent operation are little likely to spread the cancer. The authors describe the 5-year survival results in 140 cases seen between 1934 and 1946. At the time of diagnostic curettage a Y-shaped radium applicator is placed in the uterine cavity. The radium is removed when 200 mg. hours have been delivered and is re-inserted twice more at 8-day intervals. On the days when the radium is not in the uterus X-ray therapy through multiple ports is given. Antibiotics are used to prevent sepsis. When later the uterus and appendages were removed they were thoroughly studied, especially for the presence of carcinoma. Some of the cases were treated by radiation only, some by operation only, and some by combined pre-operative and postoperative radiation. The cases are divided into 4 groups according to the clinical stage of the disease, but this method makes the number in each group so small, especially when they are again subdivided according to the method of treatment, that it is not possible to draw any valid conclusion as to the value of pre-operative radiation. The one thing that does come out of the investigation is that when the removed uterus showed no residual tumour, as happened in 75 per cent of the cases, the prognosis was usually good, 87 per cent of such patients surviving 5 years. There was no correlation between histological grading according to Broder's classification and chances of survival, but survival was influenced greatly by the clinical stage of the disease.

It is evident that further planned studies are required before the value of pre-operative radiation can be assessed. *F. J. Browne*

62. **The Premalignant Phase of Endometrial Carcinoma.**

By H. Speert. *Cancer*, **5**, 927–944, Sept. 1952. 43 figs., 18 refs.

This paper is a report of a survey of 16 cases of endometrial carcinoma in which endometrial biopsy had been done at varying periods before the final diagnosis. In 3 cases carcinoma was present in the original curettings and misdiagnosed. Two cases showed normal proliferative endometrium 19 and 22 years previously. The other 11 cases had been examined between 1 and 18½ years previously and all showed degrees of atypical or adenomatous hyper-

plasia. This lesion is characterized by various combinations of epithelial budding, papilliferous projections into the lumina, pouches in the gland walls, crowding of the glands, epithelial stratification and pale staining cells. The finding of these changes up to 19 years before a diagnosis of cancer was made suggests that endometrial carcinoma may be a slowly developing disease. The author considers that the age of the patient must be considered and when found postmenopausally these changes should be considered as denoting a precancerous lesion. *R. F. Jennison*

63. **The Spread of Benign and Malignant Endometrium in the Lymphatic System with a Note on Coexisting Vascular Involvement.**

By C. T. JAVERT. *Amer. J. Obstet. Gynec.*, **64**, 780–806, Oct. 1952. 14 figs., 105 refs.

The author found pelvic lymph node involvement in 10 of 34 patients with endometriosis (29 per cent) and in 14 of 50 patients who had cancer of the endometrium (28 per cent). Ten of these cancer patients had associated endometriosis of the uterus, and 2 of these had endometriosis in the pelvic nodes. Eight of the 50 patients with endometrial cancer had cancer emboli in the blood vessels of the uterus, and 5 in the paranodal blood vessels. The incidence of malignant spread to the adnexa was only half that of spread to the pelvic nodes yet the adnexa are always removed at operation. The author therefore advocates radical hysterectomy in cancer of the corpus uteri with complete pelvic lymphadenectomy.

[This paper shows that we were wrong in thinking that the pelvic nodes usually escaped in corpus cancer, though the lumbar and aortic nodes might be involved. With pelvic nodes involved in 30 per cent of cases it is evident that complete pelvic lymphadenectomy is as necessary in cancer of the body of the uterus as in cancer of the cervix. But it is no use doing it unless it is done thoroughly. Partial removal is worse than useless just as it is in cervix cancer, because it will increase the operative mortality without improving the cure rate.] *F. J. Browne*

64. **Treatment of Endometriosis and other Gynaecologic Conditions with Large Doses of Estrogens.**

By L. M. HURXTHAL and A. T. SMITH. *New Engl. J. Med.* **247**, 339–343, Sept. 4, 1952. 1 fig., 23 refs.

The use of oestrogens in relatively high dosage for the treatment of endometriosis, uterine haemorrhage, and benign uterine tumours has been advocated by Karnaky on many occasions but it has not become popular in this country. This paper reports experiences from the Lahey Clinic using this type of therapy on 39 patients. Dosage and drugs varied but a common regimen was to give stilboestrol mg. 25 daily.

There were 25 new cases of presumed or verified endometriosis in addition to 3 which had been previously reported. Pain was relieved completely or substantially in 16 and slightly in 8 others, while there was clinical evidence of regression of nodules. Oestrogens were given to 5 patients with uterine fibroids, and in 1 case a very large tumour was found to shrink to half its size in 2 years. Four patients were treated for menorrhagia, but in 3 of these some other form of therapy was required later. Two patients were successfully treated for chronic cystic mastitis.

The authors discuss the mode of action of stilboestrol and are unwilling to believe that it acts solely by inhibition of pituitary gonadotrophins. They conclude that stilboestrol may be helpful in the treatment of endometriosis, but its usefulness is limited by the frequency of unpleasant side effects. Oestrogens are used in the temporary management of cases of excessive uterine haemorrhage, but should not be employed for an extended time. They believe that uterine fibroids and nodules of chronic cystic mastitis may decrease in size, but they require further clinical observations.

[Observations such as these are of value in contributing to a better understanding of the hormonal background of endometriosis and uterine fibroids. It is unlikely, however, as the authors point out, that oestrogens will replace surgery as the elective treatment for most patients with these disorders.] *W. G. Mills*

65. **Conservative Surgery in Ovarian Endometriosis.**

By H. FREDERIKSON. *Acta. obstet. gynec. scand.*, **32**, 24–43, 1953. 6 figs., 22 refs.

This is an exhaustive study of 126 cases of pelvic endometriosis which were observed during 10 years at the Obstetric and Gynaecological Clinic II of Gothenburg, Sweden. Out of the wealth of statistical material the following items may be of interest to the clinician.

Twenty-four point six per cent of the patients were younger than 30 years, and 6.4 per cent younger than 25 years. In 10 cases there were no symptoms, 11 patients presented themselves because of sterility; acute illness (including 2 cases of rupture of an endometrial cyst) was present 10 times; 12 patients complained of menstrual irregularities without other symptoms, while there was a history of menstrual irregularities together with pain in 18 cases; dysmenorrhoea was complained of by 75 patients, bladder and rectal symptoms were present 8 times, and in 1 case an abdominal swelling was noticed.

The method of treatment was conservative surgery, aiming at preservation of child-bearing function whenever possible; in only 15 cases bilateral salpingo-oöphorectomy was performed; hysterectomy was never carried out; adhesions were divided and all endometrial tissue was removed; resection of the utero-sacral ligaments or of the recto-vaginal septum was never done as, in the author's experience, these changes may remain unaltered for years without causing symptoms. Only 5 of the patients subjected to operation had to be operated on again; 1 because of tubal pregnancy, 1 because of uterine fibroid, and 3 for endometriosis recurring in the ovarian rests.

Among the 106 patients who underwent conservative surgery there were 77 married women under the age of 40. In 30 of these (38.9 per cent) pregnancy occurred; 8 of these patients were over 36 years old.

N. Alders

66. **The Diverse Origins of Brenner Tumours.**

By R. R. GREENE. *Amer. J. Obstet. Gynec.*, **64**, 878–898, Oct. 1952. 21 figs., 17 refs.

The most widely accepted theory of the origin of Brenner tumours is that they arise from Walthard rests, but origins from surface epithelium of the ovary and from the rete ovarii has been demonstrated. The author from a study of 14 Brenner tumours concludes that they may arise from the rete ovarii and has traced a continuity between the Brenner cells and the rete tubules in some of the 5 cases believed to be so derived. In 8 cases the tumour apparently arose from the ovarian stroma and here too it was possible to demonstrate transition stages between the stroma cells and the tumour cells. Between the individual cells of the smaller cell masses there was a reticulum which is normally found in stromal tissue. In 1 case origin from germ epithelium was suspected, as the tumorous epithelium came close to the surface but continuity with the germ epithelium could not be demonstrated in serial sections. There was no evidence of a reticulum in the tumours believed to be derived from the germ epithelium or from the rete ovarii.

F. J. Browne

67. **Dysgerminoma of the Ovary.**

By R. F. LOOKER, W. P. CALLAHAN, and F. E. BARRY. *Amer. J. Surg.*, **85**, 4–12, Jan. 1953. 10 figs., 13 refs.

Five cases of dysgerminoma of the ovary complete with follow-up studies are recorded. The authors working at St Francis Hospital, Wichita, Kansas, consider the pathogenesis of these rare tumours and believe that they arise from a totipotent cell of the undifferentiated gonadal mesenchyme or a primitive germ cell. The clinical findings and operative procedure are given in each case together with a pathological report on each specimen. Treatment was conservative in every case with removal of the affected ovary only. In the review of their results the authors believe the treatment of choice to be radical surgery and postoperative roentgen therapy.

[This is an interesting paper. The authors' theory regarding the origin of dysgerminoma is a plausible one, and while not agreeing with the traditional explanation of Meyer, it does explain the occasional occurrence of mixed tumours such as dysgerminoma with choriocarcinoma or arrhenoblastoma. Although not clear from the text the reader gets the impression that the cases described were advanced and that the outlook for the patient was poor no matter what treatment was adopted. It is not easy in view of the relative scarcity of follow-up studies of large series of cases of dysgerminoma to decide what is the best treatment. In young women anxious for a child, with a small well-encapsulated mobile tumour showing no evidence of extension, a unilateral operation may be justified.]

Declan J. Meagher

OPERATIONS

68. **The Operative Treatment of Complete Genital Prolapse in Aged Women.** (Zur operativen Behandlung des totalen Genitalprolapses im hohen Matronenalter.)

By S. KOLONJA. *Gynaecologia, Basle*, **135**, 29–36, 1953. 5 figs., 14 refs.

The operation described is a modification of that of Le Fort and Neugebauer.

Occlusion of the vaginal vault is performed as in the standard operation. In addition, in cases of stress incontinence, the urethra and base of the bladder are dissected out and a plastic repair is performed. The operation is always completed by formation of a high muscular perineum by suture of the levator ani.

The risk of the original operation was that incontinence might persist and that recurrence of prolapse might occur even after vaginal occlusion. This new operation is designed to overcome these disadvantages.

The author has performed this operation 35 times without mortality. Twenty-five of these cases have been followed up and the operation has been found to be successful.

Josephine Barnes

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